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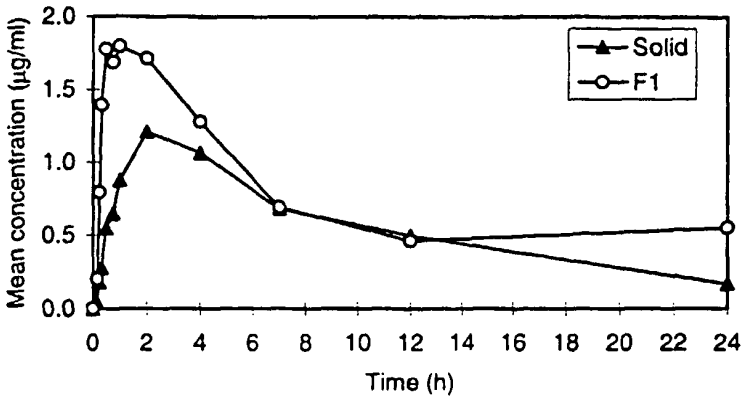
(54) Title: RAPID-ONSET FORMULATION OF A SELECTIVE CYCLOOXIGENASE-2



(57) Abstract: An orally deliverable pharmaceutical composition is provided comprising a selective cyclooxigenase-2 inhibitory drugs of low water solubility, for example celecoxib, and a glycol ether, for example diethylene glycol monoethyl ether. At least a substantial part of the drug is in dissolved or solubilized form in a solvent liquid comprising the glycol ether. The composition has rapid-onset properties and is useful in treatment of cyclooxygenase-2 mediated conditions and disorders, particularly pain. For relief of pain in headache or migraine, the composition can optionally be administered together with a vasodilator.

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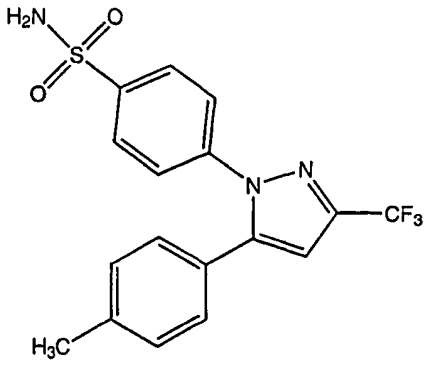
RAPID-ONSET FORMULATION OF A SELECTIVE CYCLOOXYGENASE-2 INHIBITOR

FIELD OF THE INVENTION

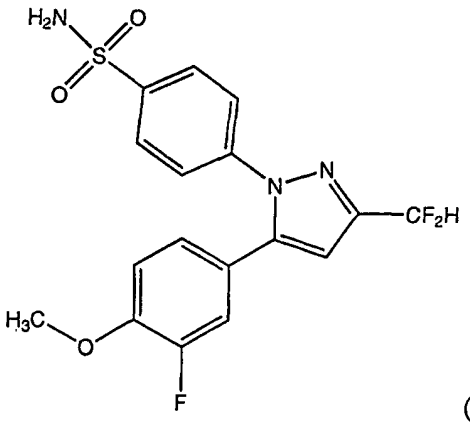
The present invention relates to orally deliverable pharmaceutical compositions containing a selective cyclooxygenase-2 (COX-2) inhibitory drug, to processes for preparing such compositions, to methods of treatment comprising orally administering such compositions to a subject in need thereof, and to the use of such compositions in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

Numerous compounds have been reported having therapeutically and/or prophylactically useful selective COX-2 inhibitory effect, and have been disclosed as having utility in treatment or prevention of specific COX-2 mediated disorders or of such disorders in general. Among such compounds are a large number of substituted pyrazolyl benzenesulfonamides as reported in U.S. Patent No. 5,466,823 to Talley *et al.*, including for example the compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as celecoxib (I), and the compound 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as deracoxib (II).



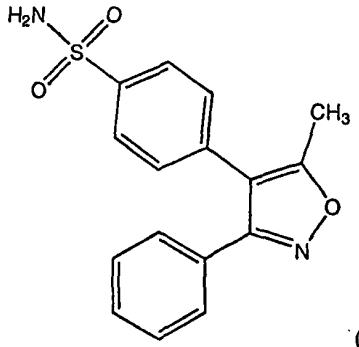
(I)



(II)

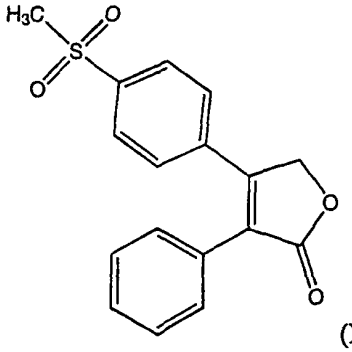
Other compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted isoxazolyl benzenesulfonamides as reported in U.S. Patent No. 5,633,272 to Talley *et al.*,

including the compound 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide, also referred to herein as valdecoxib (III).



(III)

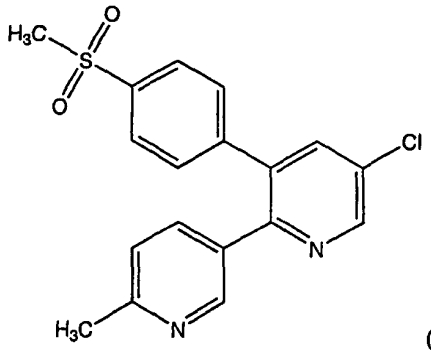
Still other compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted (methylsulfonyl)phenyl furanones as reported in U.S. Patent No. 5,474,995 to Ducharme *et al.*, including the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as rofecoxib (IV).



(IV)

U.S. Patent No. 5,981,576 to Belley *et al.* discloses a further series of (methylsulfonyl)phenyl furanones said to be useful as selective COX-2 inhibitory drugs, including 3-(1-cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one and 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one.

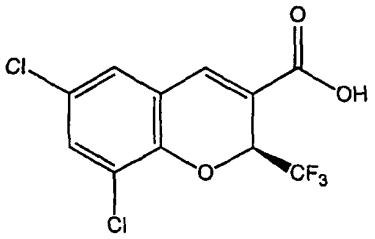
U.S. Patent No. 5,861,419 to Dube *et al.* discloses substituted pyridines said to be useful as selective COX-2 inhibitory drugs, including for example the compound 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, also referred to herein as etoricoxib (V).



(V)

European Patent Application No. 0 863 134 discloses the compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one said to be useful as a selective COX-2 inhibitory drug.

U.S. Patent No. 6,034,256 to Carter *et al.* discloses a series of benzopyrans said to be useful as selective COX-2 inhibitory drugs, including the compound (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid (VI).



(VI)

International Patent Publication No. WO 00/24719 discloses substituted pyridazinones said to be useful as selective COX-2 inhibitory drugs, including the compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

Australian Patent Applications No. 200042711, No. 200043730 and No. 200043736 disclose compositions comprising a selective COX-2 inhibitory drug, a $5HT_1$ receptor agonist and caffeine, said to be useful for treating migraine.

A need for formulated compositions of selective COX-2 inhibitory drugs, particularly rapid-onset compositions of such drugs, exists. Rapid-onset drug delivery systems can provide many benefits over conventional dosage forms. Generally, rapid-onset preparations provide a more immediate therapeutic effect than standard dosage forms. For example, in the treatment of acute pain, for example in headache or migraine, rapid-onset dosage forms would be useful to provide fast pain relief.

U.S. Patent No. 5,993,858 to Crison & Amidon discloses an excipient

formulation for increasing bioavailability of a poorly water-soluble drug. The formulation is said to be self-microemulsifying and to comprise an oil or other lipid material, a surfactant and a hydrophilic co-surfactant. The choice of surfactant is said to be less critical than the choice of co-surfactant, which reportedly should have an HLB (hydrophilic-lipophilic balance) number greater than 8. A preferred example of such a co-surfactant is said to be Labrasol™ of Gattefossé, identified as a product "comprised of medium-chain triglycerides derived from coconut oil" having HLB of 14. A formulation prepared containing 15 mg nifedipine in a size 1 (0.5 ml) capsule, *i.e.*, at a concentration of 30 mg/ml, is described as a "clear solution" at 70°C but a "semi-solid" at room temperature.

Cited in above-referenced U.S. Patent No. 5,993,858 is prior work by Farah *et al.* in which a self-microemulsifying formulation was investigated for improving *in vitro* dissolution of indomethacin. The formulation of Farah *et al.* reportedly comprised an oil phase material Gelucire™ of Gattefossé, together with a polyethylene glycol capric/caprylic glyceride product having HLB of 10, a propylene glycol laurate product having HLB of 4, and diethylene glycol monoethyl ether.

U.S. Patent No. 5,342,625 to Hauer *et al.* discloses microemulsion and microemulsifiable concentrate formulations of a cyclosporin. Such formulations are disclosed to comprise a glycol ether, for example diethylene glycol monoethyl ether.

Drugs of low water solubility are sometimes orally administered in suspension in an imbibable aqueous liquid. For example, a suspension of particulate celecoxib in a vehicle of apple juice is disclosed in co-assigned Ecuador Patent Application No. 98-2761, published on May 6, 1999 and incorporated herein by reference. Also disclosed in that application is a dilute solution of celecoxib in a mixture of PEG-400 (polyethylene glycol having an average molecular weight of about 400) and water in a 2:1 ratio by volume.

The suspension and solution compositions of Ecuador Patent Application No. 98-2761are indicated therein to have comparable bioavailability. However, following oral administration to dogs, the time taken for blood serum celecoxib concentration to reach a maximum level (T_{max}) was shorter for the solution composition than for the suspension.

Above-cited U.S. Patent No. 5,760,068 discloses that its subject pyrazolyl

benzenesulfonamide compounds, of which celecoxib and deracoxib are examples, can be administered parenterally as isotonic solutions in a range of solvents including polyethylene glycol and propylene glycol.

Above-cited U.S. Patent No. 5,633,272 discloses that its subject isoxazolyl benzenesulfonamides, of which valdecoxib is an example, can be administered parenterally as isotonic solutions in a range of solvents including polyethylene glycol and propylene glycol.

Above-cited U.S. Patent No. 5,474,995 discloses that its subject (methylsulfonyl)phenyl furanones, of which rofecoxib is an example, can be administered parenterally in an isotonic solution in 1,3-butanediol. Also disclosed therein are syrups and elixirs for oral administration, formulated with a sweetening agent such as propylene glycol.

Above-cited U.S. Patent No. 5,861,419 discloses that its subject substituted pyridines, of which etoricoxib is an example, can be administered parenterally in an isotonic solution in 1,3-butanediol. Also disclosed therein are syrups and elixirs for oral administration, formulated with a sweetening agent such as propylene glycol.

As an alternative to directly imbibable liquid formulations of a drug, it is known to encapsulate liquid formulations, for example in soft gelatin capsules or hard gelatin capsules, to provide a discrete dosage form.

Many selective COX-2 inhibitory compounds, including celecoxib, deracoxib, valdecoxib, rofecoxib and etoricoxib, have low solubility in aqueous media. In addition, some, for example celecoxib, have relatively high dose requirements. These properties present practical problems in formulating concentrated solutions of selective COX-2 inhibitory drugs for rapid-onset, oral administration. With respect to such high dose, low solubility drugs, the size of the gelatin capsule or volume of solution required to provide a therapeutic dose becomes a limiting factor. For example, a drug that has a solubility of 10 mg/ml in a given solvent and a therapeutic dose of 400 mg/day would require ingestion of 40 ml of solution. Such a volume is inconvenient or unacceptable for consumption in imbibable form; this volume also presents particular problems where a discrete dosage form is desired because capsules that contain more than about 1.0 ml to about 1.5 ml of liquid are generally considered to be too large for comfortable consumption. Alternatively, multiple capsules would

need to be ingested in order to get the required dose.

If a selective COX-2 inhibitory drug is to be formulated as a solution, highly concentrated solutions would be beneficial for several reasons. First, concentrated solutions are less costly to package and easier to transport and handle than dilute solutions. Second, as indicated above, concentrated solutions provide dose flexibility as they can be administered with or without dilution. And third, dilute drug solutions can require consumption of large volumes of fluid, which can be uncomfortable for many patient populations. For these and other reasons, therefore, if the difficulties discussed above could be overcome, it would be a much desired advance in the art to provide an effective concentrated solution formulation of a selective COX-2 inhibitory drug of low solubility, such as celecoxib, for rapid-onset indications. It would represent an especially important advance in the art to provide an effective method of treatment of acute pain, for example in headache or migraine, using such a formulation.

SUMMARY OF THE INVENTION

According to the present invention, there is now provided an orally deliverable pharmaceutical composition comprising a selective COX-2 inhibitory drug of low water solubility, at least a substantial part, for example at least about 15% by weight, of which is in dissolved or solubilized form, in a solvent liquid comprising a pharmaceutically acceptable glycol ether.

Preferably the glycol ether conforms to formula (VII):

$$R^1—O—((CH_2)_mO)_n— R^2 \qquad \text{(VII)}$$

wherein R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, C_{1-6} alkenyl, phenyl or benzyl groups, but no more than one of R^1 and R^2 is hydrogen; m is an integer of 2 to about 5; and n is an integer of 1 to about 20.

Compositions of the invention are especially useful for selective COX-2 inhibitory compounds having solubility in water lower than about 1 mg/ml.

The term "solvent liquid" herein encompasses all of the components of the liquid medium in which the selective COX-2 inhibitory drug is dissolved or solubilized including but not limited to one or more solvents, co-solvents, surfactants, co-surfactants, sweeteners, flavoring agents, colorants, *etc.*

In a presently preferred embodiment, an orally deliverable pharmaceutical

composition is provided comprising a selective COX-2 inhibitory drug of low water solubility and a solvent liquid comprising a pharmaceutically acceptable glycol ether, wherein substantially all of the drug is present in dissolved or solubilized form in the solvent liquid. In this embodiment, the solvent liquid preferably contains less than about 25% water. However, a composition of this embodiment can, if desired, be diluted with a suitable amount of water for oral administration.

In another embodiment, a composition of the invention comprises, in addition to a first portion of the drug in dissolved or solubilized form, a second portion of the drug in particulate form dispersed in the solvent liquid. In this embodiment, part of the drug is in solution and part is in suspension. Such a composition of a selective COX-2 inhibitory drug dissolved in part and dispersed in part in a solvent liquid is referred to herein as a "solution/suspension".

In a presently preferred embodiment, the solution or solution/suspension is encapsulated in one or more capsules that release the drug within a short period of time after entry into the gastrointestinal tract. The preferred encapsulation material is gelatin; however, other materials can be used. The particular mechanism of drug release is not important and can include such mechanisms as erosion, degradation, dissolution, *etc.* In this embodiment, each capsule preferably contains about 0.3 ml to about 1.8 ml (about 5 minim to about 30 minim) of solution or solution/suspension and contains a therapeutically effective amount of the selective COX-2 inhibitory drug.

Compositions of the invention have been found to resolve at least some of the difficulties alluded to above in a surprisingly effective manner. Thus, for the first time, a selective COX-2 inhibitory drug of low water solubility is presented in concentrated solution in a convenient dosage form for oral administration. A particular advantage of formulations of the invention is that following oral administration thereof, the drug is rapidly absorbed into the bloodstream. By virtue of this rapid absorption, formulations of the invention can provide rapid onset of therapeutic effect.

It can be theorized that a poorly water-soluble selective COX-2 inhibitory drug such as celecoxib can provide more rapid onset of therapeutic effect when orally administered in solution than in particulate form because the process of dissolution in

the gastrointestinal tract is not required. An even greater advantage by comparison with a solid formulation can be postulated because neither disintegration nor dissolution is required in the case of the solution composition.

Additionally, a drug administered in solution can be available for absorption higher in the alimentary tract, for example, in the mouth and esophagus, than one that becomes available for absorption only upon disintegration of the carrier formulation in the stomach or bowel.

A further advantage of solutions and other liquid dosage forms for many patients is that they are easy to swallow. A yet further advantage of imbibable liquid dosage forms such as solutions is that metering of doses is continuously variable, providing infinite dose flexibility. The benefits of ease of swallowing and dose flexibility are particularly advantageous for infants, children and the elderly.

When encapsulated, a solution or solution/suspension can provide the subject with the beneficial rapid absorption characteristics associated with liquid formulations in addition to the convenience of a discrete, easy to swallow capsule form.

Also provided by the present invention are methods for preparation of and methods for therapeutic and/or prophylactic use of compositions of the present invention.

In one embodiment, a method of analgesia is provided comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of an aminosulfonyl-comprising selective COX-2 inhibitory drug composition of the invention. In another embodiment, a method of treatment and/or prevention of headache or migraine is provided comprising orally administering, to a subject in need of such treatment or prevention, an aminosulfonyl-comprising selective COX-2 inhibitory drug composition of the invention and a vasomodulator, for example a methylxanthine, wherein the selective COX-2 inhibitory drug and the vasomodulator are administered in effective pain-relieving total and relative amounts. The selective COX-2 inhibitory drug and the vasomodulator can be administered as components of separate compositions or of a single composition. Such a single composition comprising (a) an aminosulfonyl-comprising selective COX-2 inhibitory drug, formulated as provided herein, and (b) a vasomodulator, is a further embodiment of the invention. A presently preferred methylxanthine is caffeine.

Other features of this invention will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the blood plasma concentrations of two formulations of celecoxib, F1 and a solid capsule formulation , after administration to dogs. The composition of the F1 formulation is shown in Table 2 herein.

Fig. 2 shows the blood plasma concentrations of two formulations of celecoxib, F3 and a solid capsule formulation, after administration to dogs. The composition of the F3 formulation is shown in Table 2 herein.

Fig. 3 shows the blood plasma concentrations of two formulations of celecoxib, F4 and a solid capsule formulation, after administration to dogs. The composition of the F4 formulation is shown in Table 2 herein.

Fig. 4 shows the *in vitro* dissolution profiles of five formulations: F1, F3, F4, F5 and F7. Compositions of these formulations are described in Table 2 herein.

Fig. 5 shows the *in vitro* dissolution profiles of three formulations: F8, F9 and F10. Compositions of these formulations are described in Table 2 herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides pharmaceutical compositions and dosage forms thereof suitable for oral administration, the compositions comprising a selective COX-2 inhibitory drug of low solubility in water.

Any such selective COX-2 inhibitory drug known in the art can be used, including without limitation compounds disclosed in the patents and publications listed below, each of which is individually incorporated herein by reference.

U.S. Patent No. 5,344,991 to Reitz & Li.

U.S. Patent No. 5,380,738 to Norman *et al.*

U.S. Patent No. 5,393,790 to Reitz *et al.*

U.S. Patent No. 5,401,765 to Lee.

U.S. Patent No. 5,418,254 to Huang & Reitz.

U.S. Patent No. 5,420,343 to Koszyk & Weier.

U.S. Patent No. 5,434,178 to Talley & Rogier.

U.S. Patent No. 5,436,265 to Black *et al.*

Above-cited U.S. Patent No. 5,466,823.

Above-cited U.S. Patent No. 5,474,995.

U.S. Patent No. 5,475,018 to Lee & Bertenshaw.

U.S. Patent No. 5,486,534 to Lee *et al.*

U.S. Patent No. 5,510,368 to Lau *et al.*

U.S. Patent No. 5,521,213 to Prasit *et al.*

U.S. Patent No. 5,536,752 to Ducharme *et al.*

U.S. Patent No. 5,543,297 to Cromlish *et al.*

U.S. Patent No. 5,547,975 to Talley *et al.*

U.S. Patent No. 5,550,142 to Ducharme *et al.*

U.S. Patent No. 5,552,422 to Gauthier *et al.*

U.S. Patent No. 5,585,504 to Desmond *et al.*

U.S. Patent No. 5,593,992 to Adams *et al.*

U.S. Patent No. 5,596,008 to Lee.

U.S. Patent No. 5,604,253 to Lau *et al.*

U.S. Patent No. 5,604,260 to Guay & Li.

U.S. Patent No. 5,616,458 to Lipsky *et al.*

U.S. Patent No. 5,616,601 to Khanna *et al.*

U.S. Patent No. 5,620,999 to Weier *et al.*

Above-cited U.S. Patent No. 5,633,272.

U.S. Patent No. 5,639,780 to Lau *et al.*

U.S. Patent No. 5,643,933 to Talley *et al.*

U.S. Patent No. 5,658,903 to Adams *et al.*

U.S. Patent No. 5,668,161 to Talley *et al.*

U.S. Patent No. 5,670,510 to Huang & Reitz.

U.S. Patent No. 5,677,318 to Lau.

U.S. Patent No. 5,681,842 to Dellaria & Gane.

U.S. Patent No. 5,686,460 to Nicolaï *et al.*

U.S. Patent No. 5,686,470 to Weier *et al.*

U.S. Patent No. 5,696,143 to Talley *et al.*

U.S. Patent No. 5,710,140 to Ducharme *et al.*

U.S. Patent No. 5,716,955 to Adams *et al.*

U.S. Patent No. 5,723,485 to Güngör & Teulon.

U.S. Patent No. 5,739,166 to Reitz *et al.*

U.S. Patent No. 5,741,798 to Lazer *et al.*

U.S. Patent No. 5,756,499 to Adams *et al.*

U.S. Patent No. 5,756,529 to Isakson & Talley.

U.S. Patent No. 5,776,967 to Kreft *et al.*

U.S. Patent No. 5,783,597 to Beers & Wachter.

U.S. Patent No. 5,789,413 to Black *et al.*

U.S. Patent No. 5,807,873 to Nicolaï & Teulon.

U.S. Patent No. 5,817,700 to Dube *et al.*

U.S. Patent No. 5,830,911 to Failli *et al.*

U.S. Patent No. 5,849,943 to Atkinson & Wang.

U.S. Patent No. 5,859,036 to Sartori *et al.*

Above-cited U.S. Patent No. 5,861,419.

U.S. Patent No. 5,866,596 to Sartori & Teulon.

U.S. Patent No. 5,869,524 to Failli.

U.S. Patent No. 5,869,660 to Adams *et al.*

U.S. Patent No. 5,883,267 to Rossen *et al.*

U.S. Patent No. 5,892,053 to Zhi *et al.*

U.S. Patent No. 5,922,742 to Black *et al.*

U.S. Patent No. 5,929,076 to Adams & Garigipati.

U.S. Patent No. 5,932,598 to Talley *et al.*

U.S. Patent No. 5,935,990 to Khanna *et al.*

U.S. Patent No. 5,945,539 to Haruta *et al.*

U.S. Patent No. 5,958,978 to Yamazaki *et al.*

U.S. Patent No. 5,968,958 to Guay *et al.*

U.S. Patent No. 5,972,950 to Nicolaï & Teulon.

U.S. Patent No. 5,973,191 to Marnett & Kalgutkar.

Above-cited U.S. Patent No. 5,981,576.

U.S. Patent No. 5,994,381 to Haruta *et al.*

U.S. Patent No. 6,002,014 to Haruta *et al.*

U.S. Patent No. 6,004,960 to Li *et al.*

U.S. Patent No. 6,005,000 to Hopper *et al.*

U.S. Patent No. 6,020,343 to Belley *et al.*

U.S. Patent No. 6,020,347 to DeLaszlo & Hagmann.

Above-cited U.S. Patent No. 6,034,256.

U.S. Patent No. 6,040,319 to Corley *et al.*

U.S. Patent No. 6,040,450 to Davies *et al.*

U.S. Patent No. 6,046,208 to Adams *et al.*

U.S. Patent No. 6,046,217 to Friesen *et al.*

U.S. Patent No. 6,057,319 to Black *et al.*

U.S. Patent No. 6,063,804 to De Nanteuil *et al.*

U.S. Patent No. 6,063,807 to Chabrier de Lassauniere & Broquet.

U.S. Patent No. 6,071,954 to LeBlanc *et al.*

U.S. Patent No. 6,077,868 to Cook *et al.*

U.S. Patent No. 6,077,869 to Sui & Wachter.

U.S. Patent No. 6,083,969 to Ferro *et al.*

U.S. Patent No. 6,096,753 to Spohr *et al.*

U.S. Patent No. 6,133,292 to Wang *et al.*

International Patent Publication No. WO 94/15932.

International Patent Publication No. WO 96/19469.

International Patent Publication No. WO 96/26921.

International Patent Publication No. WO 96/31509.

International Patent Publication No. WO 96/36623.

International Patent Publication No. WO 96/38418.

International Patent Publication No. WO 97/03953.

International Patent Publication No. WO 97/10840.

International Patent Publication No. WO 97/13755.

International Patent Publication No. WO 97/13767.

International Patent Publication No. WO 97/25048.

International Patent Publication No. WO 97/30030.

International Patent Publication No. WO 97/34882.

International Patent Publication No. WO 97/46524.

International Patent Publication No. WO 98/04527.

International Patent Publication No. WO 98/06708.
International Patent Publication No. WO 98/07425.
International Patent Publication No. WO 98/17292.
International Patent Publication No. WO 98/21195.
International Patent Publication No. WO 98/22457.
International Patent Publication No. WO 98/32732.
International Patent Publication No. WO 98/41516.
International Patent Publication No. WO 98/43966.
International Patent Publication No. WO 98/45294.
International Patent Publication No. WO 98/47871.
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International Patent Publication No. WO 99/01131.
International Patent Publication No. WO 99/01452.
International Patent Publication No. WO 99/01455.
International Patent Publication No. WO 99/10331.
International Patent Publication No. WO 99/10332.
International Patent Publication No. WO 99/11605.
International Patent Publication No. WO 99/12930.
International Patent Publication No. WO 99/14195.
International Patent Publication No. WO 99/14205.
International Patent Publication No. WO 99/15505.
International Patent Publication No. WO 99/23087.
International Patent Publication No. WO 99/24404.
International Patent Publication No. WO 99/25695.
International Patent Publication No. WO 99/35130.
International Patent Publication No. WO 99/61016.
International Patent Publication No. WO 99/61436.
International Patent Publication No. WO 99/62884.
International Patent Publication No. WO 99/64415.
International Patent Publication No. WO 00/01380.
International Patent Publication No. WO 00/08024.
International Patent Publication No. WO 00/10993.

International Patent Publication No. WO 00/13684.

International Patent Publication No. WO 00/18741.

International Patent Publication No. WO 00/18753.

International Patent Publication No. WO 00/23426.

Above-cited International Patent Publication No. WO 00/24719.

International Patent Publication No. WO 00/26216.

International Patent Publication No. WO 00/31072.

International Patent Publication No. WO 00/40087.

International Patent Publication No. WO 00/56348.

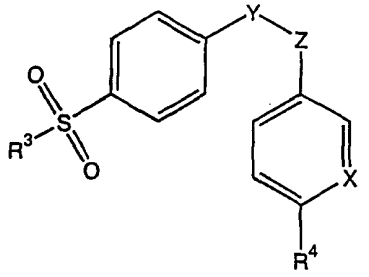
European Patent Application No. 0 799 823.

European Patent Application No. 0 846 689.

Above-cited European Patent Application No. 0 863 134.

European Patent Application No. 0 985 666.

Compositions of the invention are especially useful for compounds having the formula (VIII):



(VIII)

where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

Illustratively, celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone,

more particularly celecoxib, valdecoxib, rofecoxib and etoricoxib, and still more particularly celecoxib and valdecoxib, are useful in the method and composition of the invention.

The invention is illustrated herein with particular reference to celecoxib, and it will be understood that any other selective COX-2 inhibitory drug of low solubility in water can, if desired, be substituted in whole or in part for celecoxib in compositions herein described. For example, compositions of the invention are suitable for formulation of valdecoxib, alone or in combination with celecoxib.

Celecoxib compositions of the invention exhibit improved performance as selective COX-2 inhibitory medications. In particular, these compositions provide celecoxib to a patient at a dose and release rate sufficient to enable rapid-onset inhibition of COX-2.

Celecoxib used in pharmaceutical compositions of the present invention can be prepared by any known manner, for example in the manner set forth in above-cited U.S. Patent No. 5,466,823 or in above-cited U.S. Patent No. 5,892,053. Other selective COX-2 inhibitory drugs can be prepared by any known manner, including the manner set forth in patent publications disclosing such drugs; for example in the case of valdecoxib in above-cited U.S. Patent No. 5,633,272, and in the case of rofecoxib in above-cited U.S. Patent No. 5,474,995.

Celecoxib compositions of the present invention preferably comprise celecoxib in a daily dosage amount of about 50 mg to about 1000 mg, more preferably about 75 mg to about 400 mg, and most preferably about 100 mg to about 200 mg.

For other selective COX-2 inhibitory drugs, a daily dosage amount can be in a range known to be therapeutically effective for such drugs. Preferably, the daily dosage amount is in a range providing therapeutic equivalence to celecoxib in the daily dose ranges indicated immediately above.

Compositions of the present invention are preferably in the form of a concentrated solution that may or may not be encapsulated as a discrete article. If encapsulated, preferably a single such article or a small plurality (up to about 10, more preferably no more than about 4) of such articles is sufficient to provide the daily dose. Alternatively, compositions of the present invention are in the form of a concentrated imbibable liquid. The phrase "imbibable liquid" is used herein to refer

to an unencapsulated homogeneous flowable mass, such as a solution or solution/suspension, administered orally and swallowed in liquid form and from which single dosage units are measurably removable.

Dosage units of celecoxib compositions of the invention typically contain about 10 mg to about 400 mg of celecoxib, for example, a 10, 20, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg dose of celecoxib. Preferred dosage units contain about 50 mg to about 400 mg of celecoxib. More preferred dosage unit forms contain about 100 mg to about 200 mg of celecoxib. A particular dosage unit can be selected to accommodate the desired frequency of administration used to achieve a specified daily dose. For example, a daily dosage amount of 400 mg can be accommodated by administration of one 200 mg dosage unit, or two 100 mg dosage units, twice a day. The amount of the unit dosage form of the composition that is administered and the dosage regimen for treating the condition or disorder will depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition or disorder, the route and frequency of administration, and the particular selective COX-2 inhibitory drug selected, and thus may vary widely. It is contemplated, however, that for most purposes a once-a-day or twice-a-day administration regimen provides the desired therapeutic efficacy.

In a celecoxib composition, celecoxib can be present in the composition at a minimum concentration of about 1%, preferably about 4%, more preferably about 10%, and still more preferably about 20%, by weight. Where the selective COX-2 inhibitory drug is therapeutically effective at lower doses than celecoxib, the minimum concentration can be lower than that indicated immediately above for celecoxib; for example in the case of valdecoxib the drug can be present at a minimum concentration of about 0.1% by weight. The maximum concentration is dictated in part by solubility of the drug in the solvent liquid; it is contemplated that, where a portion of the drug is suspended in particulate form in the solvent liquid, the maximum concentration can be about 75% by weight or higher. In a composition having substantially all of the drug in dissolved or solubilized form, it is contemplated that the maximum concentration can be about 50% by weight or higher, but more typically the maximum concentration is about 35% by weight.

Compositions of the invention are useful in treatment and prevention of a very

wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants.

Contemplated compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such compositions are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Such compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

Such compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

Such compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

Such compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Such compositions are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and trauma following surgical and dental procedures.

Such compositions are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac

transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

Such compositions are useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Such compositions are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such compositions can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to

prevent polyps from forming in patients at risk of FAP.

Such compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

Because of the rapid onset of therapeutic effect that can be exhibited by compositions of the invention, these compositions have particular advantages over prior formulations for treatment of acute COX-2 mediated disorders, especially for relief of pain, for example in headache, including sinus headache and migraine.

Preferred uses for compositions of the present invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for prevention and treatment of headache and migraine, for treatment of Alzheimer's disease, and for colon cancer chemoprevention.

For treatment of rheumatoid arthritis or osteoarthritis, compositions of the invention can be used to provide a daily dose of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For treatment of Alzheimer's disease or cancer, compositions of the invention can be used to provide a daily dose of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 mg to about 400 mg, for example about 400 mg. A daily dose of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 10.7 mg/kg body weight, more preferably about 2 to about 8 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for

example about 5.3 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For pain management generally and specifically for treatment and prevention of headache and migraine, compositions of the invention can be used to provide a daily dose of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dosage unit or two 50 mg dose units twice a day or one 200 mg dosage unit, two 100 mg dosage units or four 50 mg dosage units once a day is preferred.

For selective COX-2 inhibitory drugs other than celecoxib, appropriate doses can be selected by reference to the patent literature cited hereinabove.

Besides being useful for human treatment, compositions of the invention are also useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals including rodents. More particularly, compositions of the invention are useful for veterinary treatment of COX-2 mediated disorders in horses, dogs and cats.

The present invention also is directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitor is indicated, the method comprising oral administration of one or more pharmaceutical compositions of the present invention to a patient in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the patient and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage

regimens set forth above.

Initial treatment of a patient suffering from a condition or disorder where treatment with a COX-2 inhibitor is indicated can begin with a dosage regimen as indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Patients undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine the effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective amounts of drug are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of celecoxib exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium

acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, *p*-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene,

propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition (1996), Therapeutic Category and Biological Activity Index, lists therein headed "Analgesic", "Anti-inflammatory" and "Antipyretic").

Particularly preferred combination therapies comprise use of a celecoxib composition of the invention with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof.

The compound to be administered in combination with celecoxib can be formulated separately from the celecoxib or co-formulated with the celecoxib in a composition of the invention. Where celecoxib is co-formulated with a second drug, for example an opioid drug, the second drug can be formulated in immediate-release, rapid-onset, sustained-release or dual-release form.

In an embodiment of the invention, particularly where the COX-2 mediated condition is headache or migraine, the present selective COX-2 inhibitory drug composition is administered in combination therapy with a vasomodulator, preferably a xanthine derivative having vasomodulatory effect, more preferably an alkylxanthine compound.

Combination therapies wherein an alkylxanthine compound is co-administered with a selective COX-2 inhibitory drug composition as provided herein are embraced by the present embodiment of the invention whether or not the alkylxanthine is a vasomodulator and whether or not the therapeutic effectiveness of the combination is to any degree attributable to a vasomodulatory effect. The term "alkylxanthine" herein embraces xanthine derivatives having one or more C_{1-4} alkyl, preferably methyl, substituents, and pharmaceutically acceptable salts of such xanthine derivatives. Dimethylxanthines and trimethylxanthines, including caffeine, theobromine and theophylline, are especially preferred. Most preferably, the alkylxanthine compound is caffeine.

The total and relative dosage amounts of the selective COX-2 inhibitory drug and of the vasomodulator or alkylxanthine are selected to be therapeutically and/or prophylactically effective for relief of pain associated with the headache or migraine. Suitable dosage amounts will depend on the particular selective COX-2 inhibitory drug and the particular vasomodulator or alkylxanthine selected. For example, in a combination therapy with celecoxib and caffeine, typically the celecoxib will be administered in a daily dosage amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, and the caffeine in a daily dosage amount of about 1 mg to about 500 mg, preferably about 10 mg to about 400 mg, more preferably about 20 mg to about 300 mg.

The vasomodulator or alkylxanthine component of the combination therapy can be administered in any suitable dosage form by any suitable route, preferably orally. The vasomodulator or alkylxanthine can optionally be coformulated with the selective COX-2 inhibitory drug in a single oral dosage form. Thus a solution or solution/suspension formulation of the invention optionally comprises both an aminosulfonyl-comprising selective COX-2 inhibitory drug and a vasomodulator or alkylxanthine such as caffeine, in total and relative amounts consistent with the dosage amounts set out hereinabove.

The phrase "in total and relative amounts effective to relieve pain", with respect to amounts of a selective COX-2 inhibitory drug and a vasomodulator or alkylxanthine in a composition of the present embodiment, means that these amounts are such that (a) together these components are effective to relieve pain, and (b) each component is or would be capable of contribution to a pain-relieving effect if the other component is or were not present in so great an amount as to obviate such contribution.

Compositions of the present invention comprise celecoxib and/or another selective COX-2 inhibitory drug of low solubility in a solvent liquid suitable for oral administration. The solvent liquid comprises a pharmaceutically acceptable glycol ether and optional additional components, including wetting agents, suspending agents, flocculating agents, buffers, co-solvents, colorants, sweeteners and flavoring agents, among others. Such optional additional components must be physically and chemically compatible with the other ingredients of the composition and must not be

deleterious to the recipient. Importantly, some of the above-listed classes of excipients overlap each other. Compositions of the present invention can be adapted for administration by any suitable oral route by selection of appropriate solvent liquid components and a dose of the drug effective for the treatment intended. Accordingly, components employed in the solvent liquid can themselves be solids or liquids, or both.

An imbibable celecoxib composition of the invention can be in the form of, for example, a solution, a solution/suspension, an elixir, a syrup, or any other liquid form reasonably adapted for oral administration. Such compositions can also comprise excipients selected from, for example, wetting agents, emulsifying and suspending agents, sweetening and flavoring agents, surfactants and co-surfactants.

Alternatively, a composition of the present invention can made in the form of discrete unit dosage articles, for example, soft or hard gelatin or hydroxypropylmethylcellulose (HPMC) capsules, each containing a predetermined amount of celecoxib in a solvent liquid.

Compositions of the invention can be prepared by any suitable method of pharmacy that includes the step of bringing into association the selective COX-2 inhibitory drug and the solvent liquid. In general, celecoxib compositions are prepared by uniformly and intimately admixing celecoxib with a solvent liquid and then, if desired, encapsulating the resulting solution or solution/suspension, preferably in a soft gelatin capsule. Encapsulation can be performed by any method known in the art including, but not limited to, the plate process and the rotary die process as described, for example, by Ansel *et al.* (1995) in Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., Williams & Wilkins, Baltimore, MD, pp. 176-182.

An embodiment of the present invention is a composition comprising a therapeutically effective amount of a selective COX-2 inhibitory drug of low solubility, for example celecoxib, fully dissolved or solubilized in a solvent liquid comprising a pharmaceutically acceptable glycol ether. In this embodiment, substantially no part of the drug is suspended in particulate form in the solvent liquid. Compositions of this embodiment can be formulated either in an imbibable or discrete dosage form.

Glycol ethers useful as solvents in the present invention preferably conform to

formula (VII):

$$R^1—O—((CH_2)_mO)_n— R^2 \quad \text{(VII)}$$

wherein R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, C_{1-6} alkenyl, phenyl or benzyl groups, but no more than one of R^1 and R^2 is hydrogen; m is an integer of 2 to about 5; and n is an integer of 1 to about 20. It is preferred that one of R^1 and R^2 is a C_{1-4} alkyl group and the other is hydrogen or a C_{1-4} alkyl group; more preferably at least one of R^1 and R^2 is a methyl or ethyl group. It is preferred that m is 2. It is preferred that n is an integer of 1 to about 4, more preferably 2.

Glycol ethers used in compositions of the present invention typically have a molecular weight of about 75 to about 1000, preferably about 75 to about 500, and more preferably about 100 to about 300. Importantly, the glycol ethers used in compositions of the present invention must be pharmaceutically acceptable and must meet all other conditions prescribed herein.

Non-limiting examples of glycol ethers that may be used in compositions of the present invention include ethylene glycol monomethyl ether, ethylene glycol dimethyl ether, ethylene glycol monoethyl ether, ethylene glycol diethyl ether, ethylene glycol monobutyl ether, ethylene glycol dibutyl ether, ethylene glycol monophenyl ether, ethylene glycol monobenzyl ether, ethylene glycol butylphenyl ether, ethylene glycol terpinyl ether, diethylene glycol monomethyl ether, diethylene glycol dimethyl ether, diethylene glycol monoethyl ether, diethylene glycol diethyl ether, diethylene glycol divinyl ether, ethylene glycol monobutyl ether, diethylene glycol dibutyl ether, diethylene glycol monoisobutyl ether, triethylene glycol dimethyl ether, triethylene glycol monoethyl ether, triethylene glycol monobutyl ether, tetraethylene glycol dimethyl ether, and mixtures thereof. See for example Flick (1998): Industrial Solvents Handbook, 5th ed., Noyes Data Corporation, Westwood, NJ. A presently preferred glycol ether solvent is diethylene glycol monoethyl ether, sometimes referred to in the art as DGME or ethoxydiglycol. It is available for example under the trademark Transcutol™ of Gattefossé Corporation.

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable co-solvents. Non-limiting examples of co-solvents suitable for use in compositions of the present invention include any glycol ether listed above; alcohols, for example ethanol and n-butanol; glycols not listed above, for

example propylene glycol, 1,3-butanediol and polyethylene glycol such as PEG-400; oleic and linoleic acid triglycerides, for example soybean oil; caprylic/capric triglycerides, for example Miglyol™ 812 of Huls; caprylic/capric mono- and diglycerides, for example Capmul™ MCM of Abitec; polyoxyethylene caprylic/capric glycerides such as polyoxyethylene (8) caprylic/capric mono- and diglycerides, for example Labrasol™ of Gattefossé; propylene glycol fatty acid esters, for example propylene glycol laurate; polyoxyethylene (35) castor oil, for example Cremophor™ EL of BASF; polyoxyethylene glyceryl trioleate, for example Tagat™ TO of Goldschmidt; and lower alkyl esters of fatty acids, for example ethyl butyrate, ethyl caprylate and ethyl oleate.

Many co-solvents useful in compositions of the present invention, including some of those listed above, have surfactant properties. Without being bound by theory, it is believed that certain compositions having surfactants and co-surfactants self-emulsify in the aqueous environment of the gastrointestinal tract. Preferably, surfactants and co-surfactants are selected so as to form in the gastrointestinal tract microemulsions, wherein the size of the emulsion droplets is less than about 200 nm. An illustrative preferred solvent liquid comprises diethylene glycol monoethyl ether as solvent together with polyoxyethylene glyceryl trioleate and caprylic/capric mono- and diglycerides as co-solvents.

Concentrated solution compositions of the invention preferably contain less than about 25% water. More preferably less than about 10% water is present, and most preferably no substantial amount of water is present, in a concentrated solution composition of the invention. The presence of water greatly reduces the solubility of the drug in the solvent liquid, and as a consequence seriously limits the maximum concentration at which the solution composition can be prepared. In the case of solution/suspension compositions, greater amounts of water can generally be tolerated; indeed in one embodiment of the invention the relative amounts of the drug in solution and in suspension are controlled by addition of water to reduce solubility.

Compositions of this embodiment optionally contain pharmaceutically acceptable excipients such as sweeteners, antioxidants, preservatives, etc. Through selection and combination of excipients, compositions can be provided exhibiting improved performance with respect to solvent liquid concentration, dissolution,

efficacy, flavor and overall patient compliance.

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable sweeteners. Non-limiting examples of sweeteners that can be used include mannitol, propylene glycol, sodium saccharin, acesulfame K, neotame and aspartame. Alternatively or in addition, a viscous sweetener such as sorbitol solution, syrup (sucrose solution) or high-fructose corn syrup can be used and, in addition to sweetening effects, can also be useful to increase viscosity or to retard sedimentation.

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable antioxidants. Non-limiting examples of antioxidants that can be used include ascorbic acid, sodium ascorbate, ascorbic acid palmitate, fumaric acid, malic acid, α-tocopherol, butylated hydroxyanisole, propyl gallate and sodium metabisulfite.

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable preservatives other than the antioxidants listed above. Non-limiting examples of such preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal.

Additionally, compositions of the present invention optionally comprise one or more pharmaceutically acceptable buffering agents, flavoring agents, colorants, stabilizers and/or thickeners. Buffers can be used to control pH of the formulation and can thereby modulate drug solubility. Flavoring agents can enhance patient compliance by making the composition more palatable, and colorants can provide a product with a more aesthetic and/or distinctive appearance. Non-limiting examples of colorants that can be used in compositions of the present invention include D&C Red No. 33, FD&C Red No. 3, FD&C Red No. 40, D&C Yellow No. 10, and C Yellow No. 6.

Some solvent liquids are suitable to maintain enough of a selective COX-2 inhibitory drug in solution to provide a therapeutically effective rapid-onset dose while also maintaining a portion of the drug undissolved but in suspension. The suspended portion typically provides less immediate release of the drug and so can extend the duration of therapeutic effect, although such extended duration is not a

requirement of this embodiment of the invention.

Therefore, an embodiment of the present invention is a composition comprising a therapeutically effective amount of a selective COX-2 inhibitory drug of low solubility, for example celecoxib, in part dissolved and in part dispersed in a solvent liquid comprising a pharmaceutically acceptable glycol ether. In this embodiment, part of the drug is in solution and part is in suspension. Preferably, the solvent liquid is selected such that at least about 15% of the drug is dissolved or solubilized in the solvent liquid. As indicated above, one way of modifying a solvent liquid to increase the amount of the drug in suspension as opposed to solution is to add water in the amount necessary to give the required reduction in solubility of the drug in the solvent liquid.

Depending on the relative importance of rapid onset and sustained action for the indication for which the drug is being administered, the relative proportions of dissolved and suspended drug can be varied significantly. For example, for acute pain indications, about 50% of the drug can be in solution and about 50% of the drug can be dispersed in particulate form. Alternatively, for indications demanding longer acting therapeutic effectiveness, illustratively about 20% of the drug can be dissolved and about 80% of the drug can be dispersed in particulate form.

The particulate form of the drug can be generated mechanically, for example by milling or grinding, or by precipitation from solution. Particles formed directly from such processes are described herein as "primary particles" and can agglomerate to form secondary aggregate particles. The term "particle size" as used herein refers to size, in the longest dimension, of primary particles, unless the context demands otherwise. Particle size is believed to be an important parameter affecting the clinical effectiveness of celecoxib and other selective COX-2 inhibitory drugs of low water solubility.

Particle size can be expressed as the percentage of total particles that have a diameter smaller than a given reference diameter. For example, a useful parameter is "D_{90} particle size". By definition, in a batch of a drug that has a D_{90} particle size of 60 μm, 90% of the particles have a diameter less than 60 μm.

Compositions of this embodiment of the present invention have a distribution of suspended celecoxib particle sizes such that D_{90} of the particles, in their longest

dimension, is less than about 200 μm, preferably less than about 75 μm, and more preferably less than about 25 μm. A decrease in particle size of celecoxib in accordance with this embodiment of the invention generally improves the bioavailability of the celecoxib. In addition or alternatively, suspended celecoxib particles in a composition of the invention preferably have a mean particle size less than about 10 μm, preferably about 0.1 μm to about 10 μm, for example about 1 μm.

Compositions of this embodiment can be formulated either in an imbibable or discrete dosage form. Solvents, co-solvents, sweeteners, antioxidants, preservatives, *etc.* can be selected as described above. Further, additional types of excipients can be useful in solution/suspension compositions, such as wetting agents, suspending agents and flocculating agents. Through selection and combination of excipients, solution/suspension compositions can be provided exhibiting improved performance with respect to drug concentration, physical stability, efficacy, flavor, and overall patient compliance.

Solution/suspension compositions of the present invention optionally comprise one or more pharmaceutically acceptable wetting agents. Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in the dispersion of a hydrophobic drug such as celecoxib. Non-limiting examples of surfactants that can be used as wetting agents in compositions of the present invention include benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, poloxamers (polyoxyethylene polyoxypropylene block copolymers), polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil, polyoxyethylene (20) cetostearyl ether, polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (10) oleyl ether, polyoxyethylene (40) stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate and tyloxapol, and mixtures thereof.

Solution/suspension compositions of the present invention optionally comprise one or more pharmaceutically acceptable suspending agents. Suspending agents are

used to impart increased viscosity and retard sedimentation. Suspending agents are of various classes including cellulose derivatives, clays, natural gums, synthetic gums and miscellaneous agents. Non-limiting examples of suspending agents that can be used in compositions of the present invention include acacia, agar, alginic acid, aluminum monostearate, attapulgite, bentonite, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carrageenan, carbomer, for example carbomer 910, dextrin, ethylmethylcellulose, gelatin, guar gum, HPMC, methylcellulose, ethylcellulose, ethylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, kaolin, magnesium aluminum silicate, microcrystalline cellulose, microcrystalline cellulose with carboxymethylcellulose sodium, powdered cellulose, silica gel, colloidal silicon dioxide, locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, tragacanth, xanthan gum, povidone, veegum, glycyrrhizin, pregelatinized starch, sodium starch glycolate and mixtures thereof.

In certain circumstances, it may be desirable to use flocculating agents in compositions of the invention. Solution/suspension compositions of the invention optionally comprise one or more pharmaceutically acceptable flocculating agents. Flocculating agents enable particles to link together in loose aggregates or flocs and include surfactants, hydrophilic polymers, clays and electrolytes. Non-limiting examples of flocculating agents that may be used in compositions of the present invention include sodium lauryl sulfate, docusate sodium, benzalkonium chloride, cetylpyridinium chloride, polysorbate 80, sorbitan monolaurate, carboxymethylcellulose sodium, xanthan gum, tragacanth, methylcellulose, polyethylene glycol, magnesium aluminum silicate, attapulgite, bentonite, potassium dihydrogen phosphate, aluminum chloride, sodium chloride and mixtures thereof.

An embodiment of the present invention is a concentrated composition, either a concentrated solution or a concentrated solution/suspension, that can be directly imbibed, or diluted with inert diluents and/or other carriers and imbibed; such compositions of the invention, whether diluted or not, are referred to for convenience herein as "imbibable compositions". Imbibable compositions can be prepared by any suitable method of pharmacy which includes the steps of bringing into association the selective COX-2 inhibitory drug, illustratively celecoxib, and the solvent liquid.

Celecoxib compositions of this embodiment preferably contain about 40 mg/ml to about 750 mg/ml, more preferably about 50 mg/ml to about 500 mg/ml, still more preferably about 50 mg/ml to about 350 mg/ml, and most preferably, about 100 mg/ml to about 300 mg/ml, for example about 200 mg/ml, of celecoxib.

In a further embodiment, solutions or solution/suspensions of the invention are provided which are already at a dilution suitable for direct, imbibable administration. In this embodiment, solutions or solution/suspensions of the present invention are added, in a therapeutically effective dosage amount, to about 1 ml to about 20 ml of an inert liquid. Preferably, solutions or solution/suspensions of the present invention are added to about 2 ml to about 15 ml, and more preferably to about 5 ml to about 10 ml, of inert liquid. The term "inert liquid" as used herein refers to pharmaceutically acceptable, preferably palatable liquid carriers. Such carriers are typically aqueous. Examples include water, fruit juices, carbonated beverages, *etc.*

It has been found that the demands of a rapid-onset formulation are met surprisingly well by a preparation containing a solution or solution/suspension of the present invention encapsulated in a discrete dosage unit. Therefore, another embodiment of the present invention is a concentrated composition, either a solution or solution/suspension, wherein said composition is formulated in a discrete dosage unit or units, for example capsules. Such capsules can have a soft or hard wall composed of any suitable pharmaceutical capsule wall material. Suitably, the wall can comprise gelatin and/or HPMC, optionally with one or more plasticizers. In a particular embodiment the discrete dosage units are soft gelatin capsules.

Preferably, one to about six, more preferably one to about four, and still more preferably one or two of such discrete dosage units per day provides a therapeutically effective dose of a selective COX-2 inhibitory drug.

Compositions of this embodiment are preferably formulated such that each discrete dosage unit contains about 0.3 ml to about 1.5 ml, more preferably about 0.3 ml to about 1 ml, for example about 0.8 ml or about 0.9 ml, of solution or solution/suspension.

Concentrated solutions or solutions/suspensions can be encapsulated by any method known in the art including the plate process or the rotary or reciprocating die process. By the rotary die process, liquid gelatin flowing from an overhead tank is

formed into two continuous ribbons by a rotary die machine and brought together by twin rotating dies. Simultaneously, metered fill material is injected between ribbons at the same moment that the dies form pockets of the gelatin ribbons. These pockets of fill-containing gelatin are then sealed by pressure and heat, and the capsules are served from the machine. Soft gelatin capsules may be manufactured in different shapes including round, oval, oblong, and tube-shape, among others. Additionally, by using two different ribbon colors, two-tone capsules can be produced.

EXAMPLES

Example 1

Solubility of celecoxib and valdecoxib was determined in each of several different solvent liquids as shown in Table 1, below. To determine solubility, a solid sample consisting of a known amount, typically about 50 mg, of celecoxib or valdecoxib powder was weighed into a test tube. Aliquots of a solvent liquid were then added dropwise in approximately 100 mg increments to the solid sample. The resulting mixture was vortexed and/or sonicated between aliquot additions. Aliquots of solvent liquid were added until the solvent liquid was clear, indicating that the sample was completely dissolved. Ranges in Table 1 indicate that the solubility of celecoxib or valdecoxib is between the values given but has not been more precisely determined. Solubility values preceded by the < symbol denote that, at the particular concentration shown, the mixture was still cloudy, *i.e.*, not all of the drug was fully in dissolved form.

Table 1. Solubility of celecoxib and valdecoxib in various solvent liquids

Solvent liquid	Solubility of celecoxib (mg/g)	Solubility of valdecoxib (mg/g)
propylene glycol	23 - 41	10 - 20
ethyl caprylate	25	
propylene glycol laurate	18	22
Labrasol™ [1]	64	34
propylene glycol laurate/Labrasol™ 1:1 w/w	58	42
Capmul™ MCM [2]	19 - 21	13
Miglyol™ 812 [3]	6 - 12	
Tagat™ TO [4]	24 - 40	23
Tagat™ TO/Capmul™ MCM 1:1 w/w	34 - 52	24
polyethylene glycol 400	304	50 - 85
polyethylene glycol 400/water 2:1 w/w	6	13
polyethylene glycol 400/water 1:1 w/w	<1	1
diethylene glycol monoethyl ether (DGME)	350	120
DGME/water 2:1 w/w	42	32
DGME/water 1:1 w/w	3	6
Labrasol™/DGME/propylene glycol laurate 45:45:10 w/w	313 - 325	
Labrasol™/DGME/propylene glycol laurate 40:40:20 w/w	288 - 297	130
Labrasol™/DGME/propylene glycol laurate 35:35:30 w/w	266	
Labrasol™/DGME 1:1 w/w	335	
Tagat™/Capmul™ MCM/DGME 35:35:30 w/w	212	
Tagat™/Capmul™ MCM/DGME 58:12:30 w/w	274	
tetraethylene glycol dimethyl ether	188	
triethylene glycol monoethyl ether	170	
polysorbate 80	73	
Arlacel™ 186 [5]	13	
Cremophor™ EL [6]	36	

[1] Labrasol™ = polyoxyethylene (8) caprylic/capric glycerides
[2] Capmul™ MCM = caprylic/capric mono- and diglycerides
[3] Miglyol™ 812 = caprylic/capric triglycerides
[4] Tagat™ TO = polyoxyethylene glyceryl trioleate
[5] Arlacel™ 186 = glyceryl monooleate
[6] Cremophor™ EL = polyoxyethylene (35) castor oil

The data in Table 1 illustrate advantages of the glycol ether solvent DGME for preparation of orally deliverable solutions by comparison with glycol solvents such as propylene glycol and polyethylene glycol, that are known in prior art for preparing

parenteral solutions of selective COX-2 inhibitory drugs. For example, solubility of celecoxib in DGME has been determined to be about 304 mg/g, by contrast with solubility of the same drug in propylene glycol, which is only about 23-41 mg/g. A similar approximately tenfold advantage in solubility is shown for DGME over propylene glycol in the case of valdecoxib.

Although the solubility advantage of DGME over polyethylene glycol 400 (PEG-400) as a solvent for celecoxib is less pronounced, a major advantage is seen for DGME when water is added to the solvent liquid. Solubility of celecoxib in a DGME/water mixture is significantly higher than in a PEG-400/water mixture at the same ratio of mixture ingredients. Without being bound by theory, it is believed that in the aqueous environment of the gastrointestinal tract, significantly more celecoxib will remain in solution, and hence available for immediate absorption, when delivered in a DGME-based solvent liquid than when the solvent liquid is based on PEG-400.

Example 2

Soft gelatin encapsulated formulations F1, F3, F4, F5, F7, F8, F9 and F10 were prepared having components as shown in Table 2, below. Each formulation was hand-filled into soft gelatin capsules in a final amount of 0.9 g or 0.8 g, containing 200 mg of celecoxib, per capsule, and sealed.

Table 2. Composition (mg/capsule) of soft gelatin capsule formulations

Formulation No.	F1	F3	F4	F5	F7	F8	F9	F10
celecoxib	200	200	200	200	200	200	200	200
Labrasol™ [1]	280	-	350	-	-	-	-	240
DGME	280	210	350	210	280	240	180	240
Tagat™ TO [2]	-	245	-	406	350	300	348	-
Capmul™ MCM [3]	-	245	-	84	70	60	72	-
propylene glycol laurate	140	-	-	-	-	-	-	120
Total	900	900	900	900	900	800	800	800

[1] Labrasol™ = polyoxyethylene (8) caprylic/capric glycerides
[2] Tagat™ TO = polyoxyethylene glyceryl trioleate
[3] Capmul™ MCM = caprylic/capric mono- and diglycerides

Example 3

A study was performed in order to determine pharmacokinetic properties of celecoxib formulations F1, F3 and F4 of Example 2, in male beagle dogs. Twenty four dogs (Marshall Farms, North Pose, NY) weighing approximately 7 to 9 kg and

approximately 15 to 19 months of age were randomly divided into three groups and acclimated for 5 days. The general environment was maintained as follows: temperature 18.3°C; humidity 40% or greater; approximately a 12-hour light, 12-hour dark cycle. The dogs were fasted overnight prior to dosing and for at least 4 hours post-dose. PMI Certified Canine Chow Diet # 5007 (PMI Nutrition Inc., Brentwood, MO) was available *ad libitum* to the animals throughout the study. Water from a reverse-osmosis water system was also available *ad libitum*. Each group received an oral dose of solid celecoxib in capsule form for comparison, followed by an oral dose of formulation F1, F3 or F4, in a two-way cross-over design. A five day washout period was provided between doses. Celecoxib was administered at a dose of 200 mg per animal and venous blood was collected pre-dose, and at 10, 15, 20, 30 and 45 minutes and 1, 2, 4, 7, 12 and 24 hours post-dose. Plasma was separated from blood by centrifugation at 3000 x G and samples were stored at -20°C until analysis. Concentrations of celecoxib in plasma were determined using an HPLC assay. Results are shown in Figures 1, 2 and 3.

In general, solvent liquid compositions containing diethylene glycol monoethyl ether and formulated in soft gelatin capsules exhibited superior rapid-onset pharmacokinetic profiles compared to solid capsule formulations. For example, overall, the soft gelatin capsules exhibited higher maximum plasma concentrations (C_{max}), and faster time to maximum plasma concentration (T_{max}).

Example 4

Celecoxib dissolution rates were measured *in vitro* for each of the soft gelatin capsule formulations described in Example 2, in a standard USP dissolution assay under the following conditions. USP apparatus II paddles were used to stir a dissolution medium (1 liter water containing 1% sodium dodecyl sulfate) at a speed of 75 rpm and a temperature of 37°C. After stirring for 90 minutes, an infinity time point was achieved by stirring at 250 rpm. The medium was then filtered through 10mm Van-Kel filters. Samples were analyzed for celecoxib via UV detection. Dissolution rates for each of the formulations are shown in Figures 4 and 5.

It will be understood that *in vitro* dissolution rates obtained by the above procedure are not necessarily indicative in absolute terms of the process of release of celecoxib from an encapsulated solution in the gastrointestinal tract. However, it is

believed that in relative terms a formulation exhibiting more rapid or complete dissolution in this assay will provide faster release in the gastrointestinal tract, and thereby faster onset of therapeutic effect.

It will be noted in Figure 4 that among the 900 mg capsule formulations containing 200 mg celecoxib, the most rapid and complete *in vitro* dissolution was obtained with F3, wherein the solvent liquid comprises DGME accompanied by two co-solvents, polyoxyethylene glyceryl trioleate (Tagat™ TO) and caprylic/capric mono- and diglycerides (Capmul™ MCM).

WHAT IS CLAIMED IS:

1. An orally deliverable pharmaceutical composition comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility and a solvent liquid that comprises a pharmaceutically acceptable glycol ether, wherein at least a substantial part of the drug is in dissolved or solubilized form in the solvent liquid.

2. The composition of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is selected from celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone.

3. The composition of Claim 1 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

4. The composition of Claim 3 that comprises one or more dosage units each comprising about 10 mg to about 400 mg of celecoxib.

5. The composition of Claim 3 having a concentration of celecoxib of about 1% to about 75% by weight.

6. The composition of Claim 1 wherein the glycol ether is of formula

$$R^1—O—((CH_2)_mO)_n— R^2$$

wherein R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, C_{1-6} alkenyl, phenyl or benzyl groups, no more than one of R^1 and R^2 being hydrogen; m is an integer of 2 to about 5; and n is an integer of 1 to about 20.

7. The composition of Claim 6 wherein the glycol ether is selected from ethylene glycol monomethyl ether, ethylene glycol dimethyl ether, ethylene glycol monoethyl ether, ethylene glycol diethyl ether, ethylene glycol monobutyl ether, ethylene glycol dibutyl ether, ethylene glycol monophenyl ether, ethylene glycol monobenzyl ether, ethylene glycol butylphenyl ether, ethylene glycol terpinyl ether, diethylene glycol monomethyl ether, diethylene glycol dimethyl ether, diethylene glycol monoethyl ether, diethylene glycol diethyl ether, diethylene

glycol divinyl ether, ethylene glycol monobutyl ether, diethylene glycol dibutyl ether, diethylene glycol monoisobutyl ether, triethylene glycol dimethyl ether, triethylene glycol monoethyl ether, triethylene glycol monobutyl ether, tetraethylene glycol dimethyl ether, and mixtures thereof.

8. The composition of Claim 6 wherein the glycol ether is diethylene glycol monoethyl ether.

9. The composition of Claim 1 wherein substantially all of the selective cyclooxygenase-2 inhibitory drug present in the composition is in dissolved or solubilized form.

10. The composition of Claim 9 wherein the glycol ether is diethylene glycol monoethyl ether and the solvent liquid further comprises one or more excipients selected from polyoxyethylene (8) caprylic/capric glycerides, caprylic/capric mono- and diglycerides, propylene glycol laurate and polyoxyethylene glyceryl trioleate.

11. The composition of Claim 9 wherein the solvent liquid comprises diethylene glycol monoethyl ether, caprylic/capric mono- and diglycerides, and polyoxyethylene glyceryl trioleate.

12. The composition of Claim 1 wherein a first substantial portion of the selective cyclooxygenase-2 inhibitory drug present in the composition is in dissolved or solubilized form, and the composition further comprises a second portion of the selective cyclooxygenase-2 inhibitory drug in particulate form dispersed in the solvent liquid.

13. The composition of Claim 1 that is an unencapsulated imbibable liquid.

14. The composition of Claim 1 that comprises one or more discrete dosage units, wherein a therapeutically effective amount of the selective cyclooxygenase-2 inhibitory drug is contained in one to a small plurality of said dosage units.

15. The composition of Claim 14 wherein the dosage units are liquid-filled capsules having a wall.

16. The composition of Claim 15 wherein the wall comprises gelatin and/or

hydroxypropylmethylcellulose.

17. The composition of Claim 1 that further comprises a vasomodulator, wherein the selective cyclooxygenase-2 inhibitory drug and the vasomodulator are present in total and relative amounts effective to relieve pain in headache or migraine.

18. The composition of Claim 1 that further comprises an alkylxanthine compound, wherein the selective cyclooxygenase-2 inhibitory drug and the alkylxanthine compound are present in total and relative amounts effective to relieve pain in headache or migraine.

19. The composition of Claim 18 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

20. The composition of Claim 18 wherein the alkylxanthine compound is caffeine.

21. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of any of Claims 1-20.

22. A method of analgesia comprising orally administering, to a subject in need of analgesia, an effective pain-relieving amount of a composition of any of Claims 1-20 comprising a selective cyclooxygenase-2 inhibitory drug.

23. The method of Claim 22 wherein the subject suffers from headache or migraine and wherein there is further orally administered to the subject a vasomodulator, the selective cyclooxygenase-2 inhibitory drug and the vasomodulator being administered in total and relative amounts effective to relieve pain in the headache or migraine.

24. The method of Claim 22 wherein the subject suffers from headache or migraine and wherein there is further orally administered to the subject an alkylxanthine compound, the selective cyclooxygenase-2 inhibitory drug and the alkylxanthine compound being administered in total and relative amounts effective to relieve pain in the headache or migraine.

25. The method of Claim 24 wherein the alkylxanthine compound is coformulated

with the selective cyclooxygenase-2 inhibitory drug.

26. The method of Claim 24 wherein the alkylxanthine compound is selected from caffeine, theophylline and theobromine.

27. The method of Claim 24 wherein the alkylxanthine compound is caffeine.

5

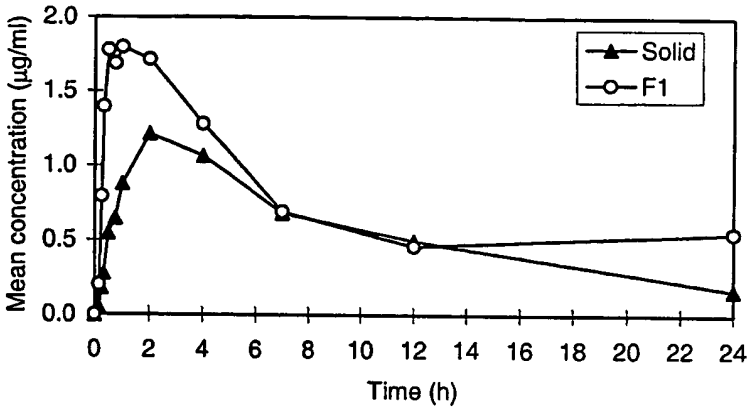


Fig. 1

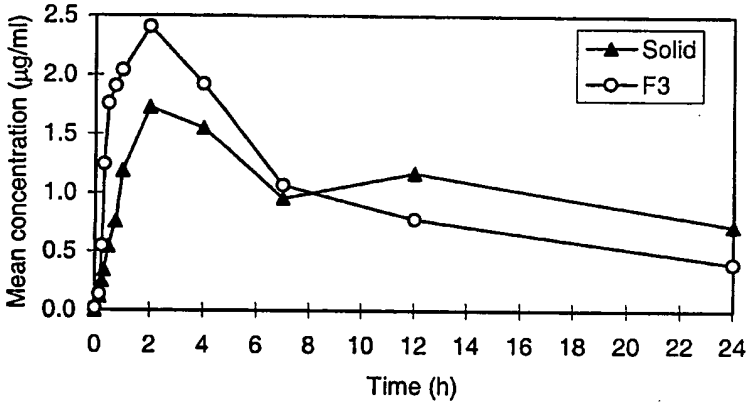


Fig. 2

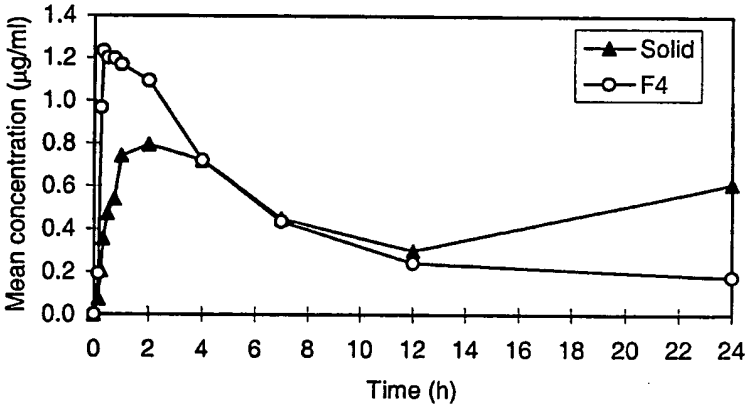


Fig. 3

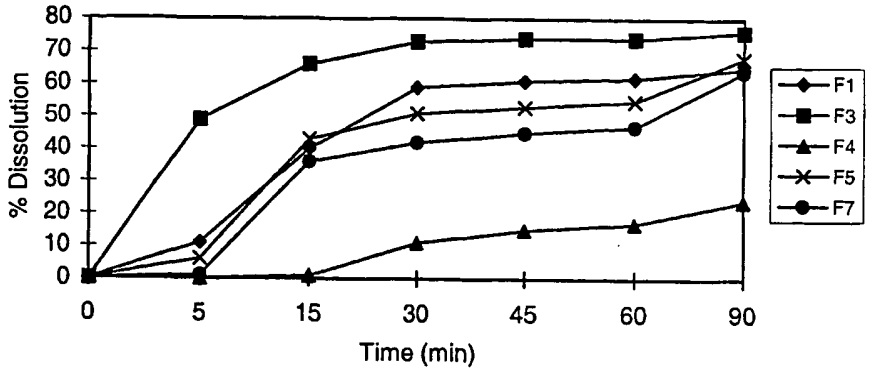

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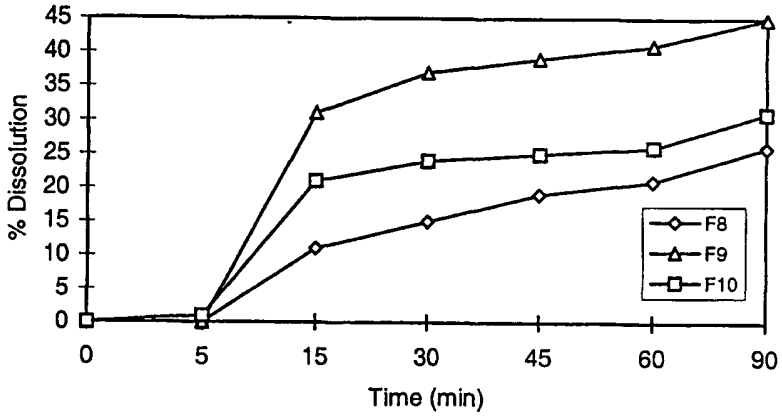
Fig. 4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Time (min)
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F9
F10

Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/12434

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 A61K31/42 A61K9/48 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 13, 30 November 1999 (1999-11-30) & JP 11 228448 A (PANACEA BIOTEC LTD), 24 August 1999 (1999-08-24) abstract	1,2, 6-11,13, 15,21,22
A	EP 0 863 134 A (MERCK FROSST CANADA) 9 September 1998 (1998-09-09) cited in the application claims 1,8,13-16 examples 5,7 page 3, line 51 page 4, line 54 -page 5, line 6	1-27

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2001	05/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 01/12434

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 756 529 A (P. C. ISAKSON ET AL.) 26 May 1998 (1998-05-26) claims 1,4-8 column 96, line 20 - line 58 column 97, line 12 - line 21	1,2, 6-11,13, 15,21,22
A	US 5 993 858 A (J. R. CRISON ET AL.) 30 November 1999 (1999-11-30) cited in the application claims column 2, line 21 - line 32 column 4, line 4 -column 5, line 26	1,2, 6-11,13, 15,21,22
A	WO 00 09117 A (EDKO) 24 February 2000 (2000-02-24) claims examples	1,2, 6-11,13, 15,21,22
A,P	WO 01 01960 A (LIPOCINE) 11 January 2001 (2001-01-11) claims examples 7-44,7-45	1,2, 6-11,13, 15,21,22

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/US 01/12434

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Jesse Fecker

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NOVEMBER

DATE/TIME	SPEAKER	TOPIC
Nov. 21st /12:30	Borden Ladner & Gervais (Christine Collard & David Conn)	Issues Relating to Canadian Patent Law
Nov. 28th	**NO SEMINAR**	

DECEMBER

DATE/TIME	SPEAKER	TOPIC
Dec. 5th /12:30	Anne Stein	Library Services
Dec. 12th /12:30	Joe Maraia	Recent Case
Dec. 19th /12:30	Pam Torpey	Recent Case
Dec. 26th	**NO SEMINAR**	

JANUARY 2003

DATE/TIME	SPEAKER	TOPIC
Jan. 9th /12:30	Kevin Shaughnessy	Recent Case
Jan. 16th /12:30	Deirdre Sanders	Recent Case

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Pharmacokinetics of Celecoxib after Oral Administration in Dogs and Humans: Effect of Food and Site of Absorption

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ABSTRACT

Celecoxib pharmacokinetics was evaluated after single and multiple oral dosing; after dosing in a solution and as a solid; with and without food; and after administration into different sites of the GI tract using dog. After oral dosing in a solution, celecoxib was rapidly absorbed and reached maximum concentrations by 1 h; absorption was delayed another 1 to 2 h when administered as a solid. The absolute bioavailability of celecoxib was higher when given as a solution (64–88%) compared with capsule (22–40%). The absorption of celecoxib given in a capsule was delayed by food, although systemic exposure increased by 3- to 5-fold. The systemic availability of celecoxib given intragastrically in solution was similar to that obtained following direct instillation into the duodenum, jejunum, or colon through a chronic intestinal access port. Collectively, these data suggest that celecoxib is a highly permeable drug that can be absorbed throughout the GI tract and that dissolution may be a rate-limiting factor for absorption from solid dosage forms. Unlike dogs, celecoxib given to humans with a high fat meal exhibits only a slight increase in $AUC_{0-\infty}$ (11%) that is not clinically significant with regard to safety or efficacy. In humans, a lower dose and a longer GI residence time may promote the opportunity for absorption of a poorly soluble drug such as celecoxib that can be absorbed throughout the GI tract. This would minimize the effect of food on absorption; as such, patients with arthritis can be given celecoxib with or without food.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the signs and symptoms of inflammation associated with rheumatoid arthritis and osteoarthritis. However, side effects related to gastrointestinal, renal, and platelet function sometimes have important clinical limitations on NSAID use (Borda and Koff, 1992). Since the early 1970s, the mechanism of action of NSAIDs has been attributed to the blockade of the production of prostaglandins via inhibition of the enzyme cyclooxygenase (Smith and Willis, 1971; Vane, 1971). The existence of two cyclooxygenase(s), designated COX-1 and COX-2, has been reported (Masferrer et al., 1994; Needleman and Isakson, 1997). COX-1, the constitutive form, is expressed in most tissues, including the gastrointestinal tract and platelets and produces prostaglandins necessary for normal physiological function (Kujubu et al., 1991; Xie and Chipman, 1991). COX-2 is inducible and is predominantly expressed in association with inflammation (Raz et al., 1988; Masferrer et al., 1994). It has been demonstrated that COX-2-specific inhibitors will have anti-inflammatory activity without the associated GI side effects of traditional NSAIDs (Simon et al., 1999; Silverstein et al., 2000). Celecoxib is a marketed COX-2-specific inhibitor that does not inhibit COX-1 at the clinical dose used to treat osteoarthritis and rheumatoid arthritis (Isakson et al., 1998).

Celecoxib (Fig. 1) is extensively metabolized in humans and is excreted primarily as metabolites (Paulson et al., 2000a). The methyl group of celecoxib is oxidized to the hydroxymethyl metabolite, followed by further oxidation of the hydroxyl metabolite to the carboxylic acid. Glucuronide conjugation of the carboxylic acid metabolite is a minor pathway of elimination in humans.

The metabolism of celecoxib across several species, including mouse, rat, rabbit, dog, and monkey, has been shown to be similar to human metabolism with hydroxylation as the primary pathway of elimination (Paulson et al., 2000b,c). Dogs are unique compared with the other species in that there is a polymorphism in the canine metabolism of celecoxib with existence of two phenotypes identified as extensive (EM) or poor (PM) metabolizers (Paulson et al., 1999).

There are numerous reviews on the effects of food on the pharmacokinetics of drugs (Karim, 1996; Welling, 1996; Fleisher et al., 1999; Singh, 1999). Food most often affects

ABBREVIATIONS: NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; EM, extensive metabolizer; PM, poor metabolizer; GI, gastrointestinal; CIAP, chronic intestinal access port; C_{max}, observed peak plasma concentration; T_{max}, time to peak plasma concentration; AUC, area under the plasma concentration-time curve; BA, bioavailability; IG, intragastrically.

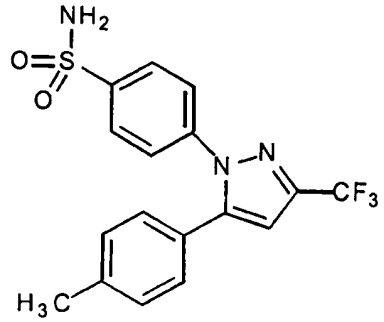

Fig. 1. Chemical structure of celecoxib.

drug absorption and metabolism. Administration of drugs with food may reduce, delay, increase, or have no effect on drug absorption. Food can affect GI physiology (gastric emptying time, acid secretion, blood flow, intestinal motility, bile secretion, and enzyme secretion), and thereby drug absorption. The potential for a food-drug interaction is dependent upon the region of the GI tract where the drug is absorbed. Drugs only absorbed in the upper intestine have a greater potential for reduced absorption when given with food (Fleisher et al., 1999).

The objective of the present study was to examine the pharmacokinetics of celecoxib after oral single and multiple dose administration. In addition, the effects of food, different dose forms and site-specific administration on celecoxib bioavailability were studied. Also, the appropriateness of the dog as a model for human celecoxib absorption was addressed.

Materials and Methods

Chemicals. Celecoxib was synthesized at G.D. Searle (Skokie, IL). Investigational celecoxib drug supplies were provided by G.D. Searle. All other reagents and solvents were of analytical grade. The neat chemical was micronized by ball-milling. Formulated capsules were composed of celecoxib sieved through an 840-μm screen and wet granulated with water-soluble diluents. The particle size for the neat chemical and formulated chemical was 5 μm.

Dogs. Male and female pure-bred beagle dogs weighing between 7 and 14 kg were used (Hazleton Research Products, Inc., Cumberland, VA; HRP, Kalamazoo, MI). Dogs were screened for population phenotype (poor or extensive metabolizer) as previously described (Paulson et al., 1999). The animals were housed unrestrained, individually in stainless steel cages, and were allowed access to food (PMI Feeds, Inc., Richmond, IN) and water ad libitum unless otherwise indicated.

Single Dose Pharmacokinetics in Dogs. Dogs (n = 12) were fasted overnight before dosing and were given access to food approximately 4 h postdose. Dogs were administered celecoxib i.v. and orally in a solution, as neat chemical capsule and formulated in a capsule in a nonrandomized, crossover design at a dose of 5 mg/kg. The i.v. and oral dose solutions were prepared in a vehicle of polyethylene glycol 400/saline (2:1, v/v) at a concentration of 5 mg/ml for the i.v. dose and a concentration of 2 mg/ml for the oral dose. The animals were dosed at approximately 8 AM. There was at least a 7-day washout period between each dose. Venous blood (approximately 3 ml) from the jugular vein was collected into chilled tubes containing sodium heparin from the animals at approximately 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 2.5, 3.5 6, 8 12, 18, 24, and 48 h after the i.v. dose and at 0.25, 0.5, 1, 1.5, 2, 2.5,3, 4, 6, 8, 12, and 24 h after the oral doses.

Multiple Dose Pharmacokinetics in Dogs. Beagle dogs were administered celecoxib in a gelatin capsule at 7.5 mg/kg b.i.d., 12.5 mg/kg b.i.d., 17.5 mg/kg b.i.d., and 25 mg/kg once a day for 13 weeks in one study and for 1 year in a separate study. The animals administered 7.5, 12.5, and 17.5 mg/kg celecoxib were given two doses approximately 12 h apart. Animals were fasted overnight before the initial dose and were given access to food approximately 4 h postdose. Blood was collected at 0.5, 1, 2, 3, 5, 7, 12, 13, 14, 15, 18, and 24 h after the first dose for the 7.5-, 12.5-, and 17.5-mg/kg dose groups and at 0.5, 1, 1.5, 2, 2.5, 3.5, 5, 7, and 24 h postdose for the 25-mg/kg dose group. The blood samples were collected on the first day of dosing for each study, at 6 and 13 weeks in the 13-week study and at 6 months and 1 year in the 1-year study.

Food Effect Study in Dogs. Beagle dogs (n = 3 EM; n = 3 PM) were administered celecoxib (5 mg/kg) as neat chemical in a gelatin capsule under four different dietary conditions in a nonrandomized, crossover design. For the first period, dogs were fasted overnight before dosing. For the second period, dogs were given a diet low in fat followed immediately by the dose. The low-fat diet consisted of a slice of toasted white bread spread with 0.5 ounce of jelly, 8 ounces of skim milk, and 6 ounces of orange juice. For the third period, dogs were given a medium-fat diet followed immediately by the dose. The medium-fat diet consisted of one slice of toasted white bread with 0.5 ounce each of peanut butter and jelly, 1 ounce of dry cereal (cornflakes), 8 ounces of skim milk, 6 ounces of orange juice, and one banana. For the fourth period, dogs were given a high-fat diet followed immediately by the dose. The high-fat diet consisted of two slices of toasted white bread spread with 1.2 ounces of butter, two eggs fried in butter, two slices of cooked bacon, 2 ounces of hash brown potatoes fried in butter, and 8 ounces of whole milk. All diets were homogenized and were administered either in a bowl or with a syringe. There was a washout period of approximately 7 days between each phase. Blood samples were collected from the jugular vein into chilled tubes containing sodium heparin at 0.25, 0.5, 1, 1.5,, 2.5, 3, 4, 6, 8, 12, 18, and 24 h after each dose administration.

Chronic Intestinal Access Port Studies in Dogs. Four female beagle dogs (n = 2 poor metabolizers; n = 2 extensive metabolizers) were surgically prepared and three chronic intestinal access ports (CIAP) directly accessible to the upper duodenum, jejunum, and colon were permanently implanted (Meunier et al., 1993). Dogs were allowed to recover from the surgical procedure before administration of celecoxib. Celecoxib was administered to each dog in a nonrandomized, crossover design at four different periods either intragastrically or directly through a CIAP into the duodenum, jejunum or colon. Dogs were fasted overnight before administration of celecoxib. The celecoxib was administered in a solution of polyethylene glycol 400/saline (2:1) at doses of 10 mg/kg. There was a washout period of at least 1 week between each dose administration. Blood samples (approximately 2.5 ml) were collected into chilled tubes containing sodium heparin at predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 12, and 24 h after each dose administration.

Food Effect Study in Healthy Subjects. Twenty-four, healthy adults (n = 5 female; n = 19 male) were administered a single dose of celecoxib capsule (200 mg) under fasting conditions (treatment A) and immediately after a high-fat breakfast (treatment B) in an open label, randomized crossover study. There were at least 7 days between the administration of the two treatments. Subjects fasted for at least 8 h before their scheduled treatment regimen. For treatment A, subjects were administered a 200-mg celecoxib capsule under fasting conditions. For treatment B, subjects were administered a 200-mg celecoxib capsule immediately after a high-fat breakfast. The high-fat breakfast consisted of two slices of toasted white bread with butter, two eggs fried in butter, two slices of bacon, 2 ounces of hash browned potatoes, and 8 ounces of whole milk. The nutritional content of the high-fat breakfast consisted of 33 g of protein, 75 g of fat, 58 g of carbohydrates, and 1000 calories. Each dose of celecoxib was administered with 210 ml of room temperature water. Subjects remained upright for 4 h after the celecoxib dose administration. A

TABLE 1
Mean ± S.E.M. pharmacokinetic parameters of celecoxib after single i.v. administration at 5 mg/kg to dogs

Dose	No. of Dogs	Phenotype	Vd_{ss}	$t_{1/2}$	Cl	$AUC_{0-\infty}$
mg/kg			*l/kg*	*h*	*ml/min/kg*	*(μg/ml)h*
5	6	EM	1.9 ± 0.08	1.3 ± 0.2	21.8 ± 2.3	4.04 ± 0.44
5	6	PM	2.3 ± 0.06	5.1 ± 0.5	7.4 ± 0.5	11.5 ± 0.75

Vd_{ss}, apparent volume of distribution at steady state; Cl, clearance.

TABLE 2
Mean ± S.E.M. pharmacokinetic parameters for celecoxib following single oral administration to dogs

Dose	Formulation	*n*	C_{max}	T_{max}	$AUC_{0-\infty}$	BA
mg/kg			*μg/ml*	*h*	*(μg/ml)h*	*%*
EM dogs						
5	Solution	3	0.82 ± 0.22	0.67 ± 0.17	2.63 ± 0.59	63.7 ± 10.5
5	Neat chemical	6	0.23 ± 0.05	1.5 ± 0.2	0.95 ± 0.33	21.7 ± 5.4
5	Formulated capsule	6	0.28 ± 0.02	1.3 ± 0.1	0.97 ± 0.1	24.0 ± 1.7
PM dogs						
5	Solution	3	1.32 ± 0.03	0.5 ± 0	10.5 ± 1.6	88.2 ± 5.8
5	Neat chemical	6	0.58 ± 0.15	3.3 ± 1.7	4.4 ± 0.8	39.4 ± 7.0
5	Formulated capsule	6	0.32 ± 0.04	1.3 ± 1.1	3.0 ± 0.3	27.2 ± 3.7

7-ml blood sample was collected for the measurement of celecoxib at 15 min predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h postdose. A standard low-fat lunch was served after the 4-h postdose blood sample.

Assay for Plasma Celecoxib. Plasma was prepared by centrifugation of blood. Plasma was stored frozen at −20°C until analysis for concentration of celecoxib. The celecoxib concentration was determined using a high performance liquid chromatography assay with fluorescence detection for dog plasma (Paulson et al., 1999) and for human plasma (Paulson et al., 2000).

Pharmacokinetic Calculations. The plasma celecoxib concentration-time curves after i.v. and oral single dose administration were analyzed using noncompartmental kinetics (Gilbaldi and Perrier, 1982). The C_{max} is the maximum plasma concentration observed. The T_{max} is the time at which C_{max} occurs. The AUC_{0-t} is the area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration after each single dose, calculated using the linear trapezoidal rule. The $AUC_{0-\infty}$ is the area under the plasma concentration-time curve from time 0 to infinity, calculated as AUC_{0-t} plus $-C/\beta$, where β is the slope from the linear regression of the natural log (concentration) versus time during the terminal phase. The $AUC_{0-24\ h}$ after multiple dose administration was also calculated by the linear trapezoidal rule. The absolute bioavailability was calculated as ($AUC_{0-\infty}$ oral/$AUC_{0-\infty}$ i.v.) × 100.

Statistics. The pharmacokinetic parameters for the animal studies were compared using ANOVA. An ANOVA model with factors for sequence, subject with sequence, period, and treatment was used to compare pharmacokinetic variables between treatment groups.

Results

Intravenous and Oral Single Dose Studies in Dogs. The plasma pharmacokinetic parameters after single i.v. or oral administration of celecoxib to EM or PM dogs are listed in Tables 1 and 2. After i.v. administration, the celecoxib $AUC_{0-\infty}$ is greater, $t_{1/2}$ is longer and clearance is lower in PM versus EM dogs. Celecoxib is well absorbed when administered as a solution with absolute bioavailability (BA) of 63.7 and 88.2% in EM and PM dogs, respectively. The absolute bioavailability of celecoxib is 3- to 4-fold greater when administered as a solution compared with when the drug is administered as neat chemical or formulated in a gelatin capsule. The absorption of celecoxib is also faster when administered as a solution compared with when the drug is administered as neat chemical or formulated in a gelatin capsule with the respective T_{max} of 0.67, 1.5, and 1.3 h for EM dogs and 0.5, 3.3, and 1.3 h for PM dogs.

Multiple Dose Studies in Dogs. The $AUC_{0-24\ h}$ and C_{max} values for EM and PM dogs administered celecoxib (7.5, 12.5, and 17.5 mg/kg b.i.d.) for up to 1 year are shown in Figs. 2 and 3, respectively. The $AUC_{0-24\ h}$ and C_{max} values increased approximately proportional with increasing dose. The $AUC_{0-24\ h}$ and C_{max} values remained nearly constant over the 1-year dosing period with no consistent increase or decrease with time. The systemic exposure to celecoxib as measured by $AUC_{0-24\ h}$ or C_{max} was greater in PM compared with EM dogs.

Food Effect Study in Dogs. Figure 4 shows the plasma concentration-time profiles for celecoxib after oral administration to both fed and fasted dogs. The pharmacokinetic parameters of celecoxib in the fed and fasted state are listed in Table 3. The administration of celecoxib in the presence of food resulted in a 3- to 5-fold increase in the extent of absorption of drug as measured by changes in C_{max} and $AUC_{0-\infty}$. The administration of celecoxib in presence of food delayed absorption in all dogs except one PM animal. This animal exhibited a "double peak" plasma concentration curve. The first peak occurred at 3 h and the second peak, the C_{max}, occurred at 18 h. The mean T_{max} without this animal was 2.3 h.

Food Effect Study in Healthy Subjects. Figure 5 shows the plasma concentration-time profiles for celecoxib after oral administration of a 200-mg celecoxib capsule to healthy subject under fasting conditions and immediately after a high-fat breakfast. The pharmacokinetic parameters of celecoxib are listed in Table 4. The consumption of dietary fat before dosing with 200-mg celecoxib capsules increased T_{max} and C_{max} values 140% compared with the values obtained after dosing to the same subjects under fasting conditions. The relative bioavailability of celecoxib following administration of a 200-mg celecoxib capsule following a high-fat breakfast was 110% compared with administration of the drug under fasting conditions. Based on the ratios and the 95% confi-

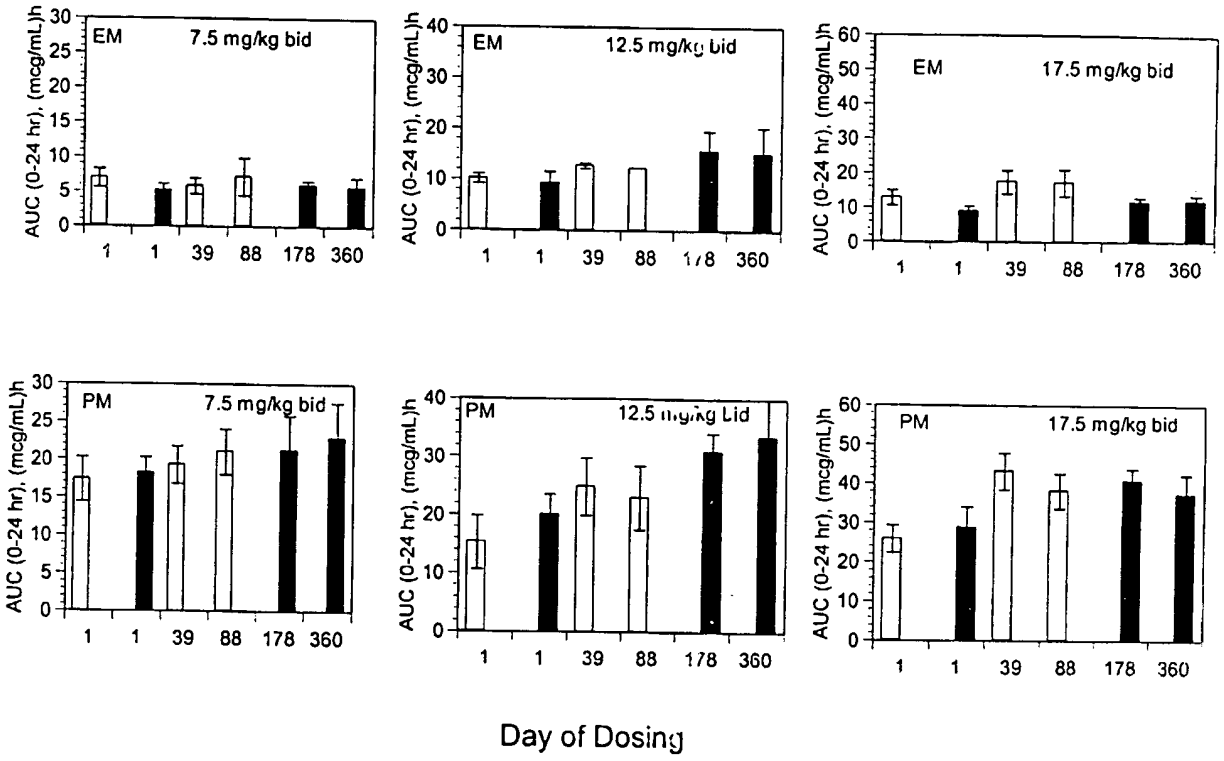

Fig. 2. Mean ± S.E.M. of $AUC_{0-24\ h}$ of celecoxib in EM and PM dogs dosed orally at 7.5 mg/kg (b.i.d.), 12.5 mg/kg (b.i.d.), and 17.5 mg/kg (b.i.d.) for 1 year. The open columns are results from a 13-week study and the closed columns are results from a separate 1-year study.

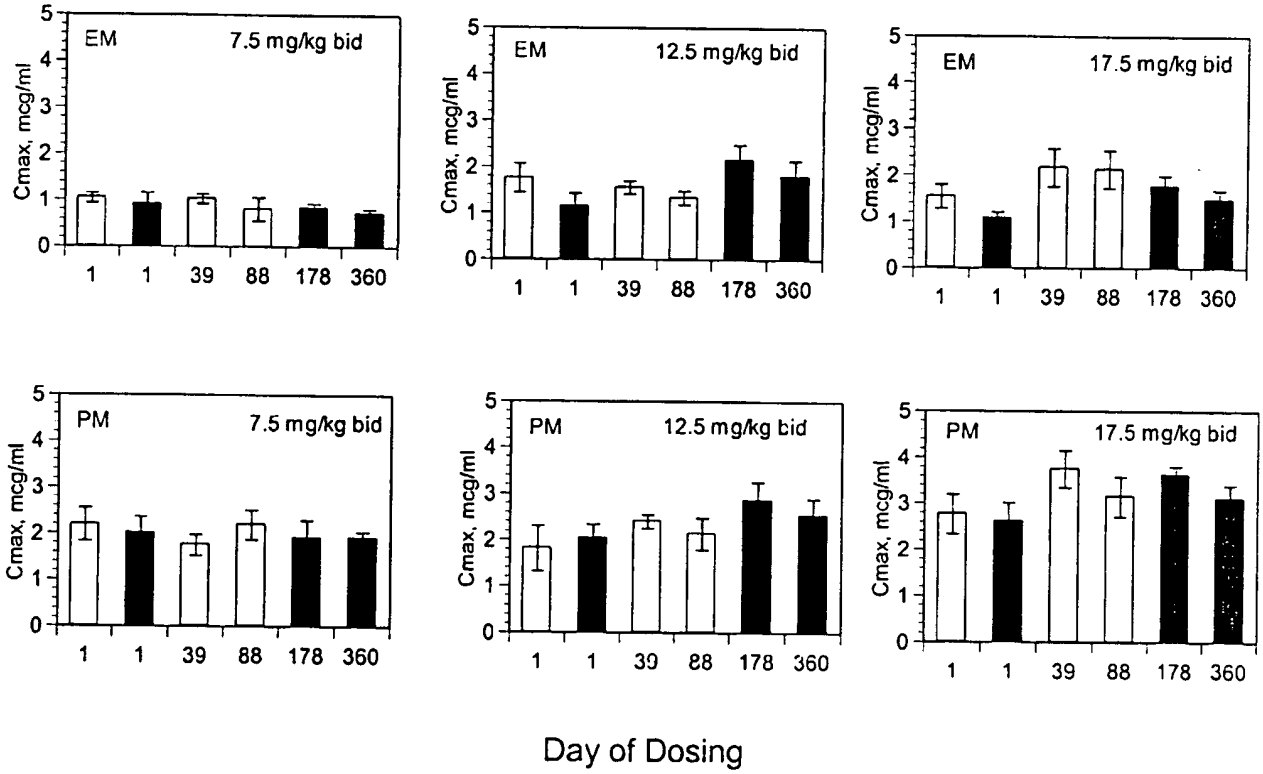

Fig. 3. Mean ± S.E.M. of C_{max} of celecoxib in EM and PM dogs dosed orally at 7.5 mg/kg (b.i.d.), 12.5 mg/kg (b.i.d.), and 17.5 mg/kg (b.i.d.) for 1 year. The open columns are results from a 13-week study and the closed bars are results from a separate 1-year study.

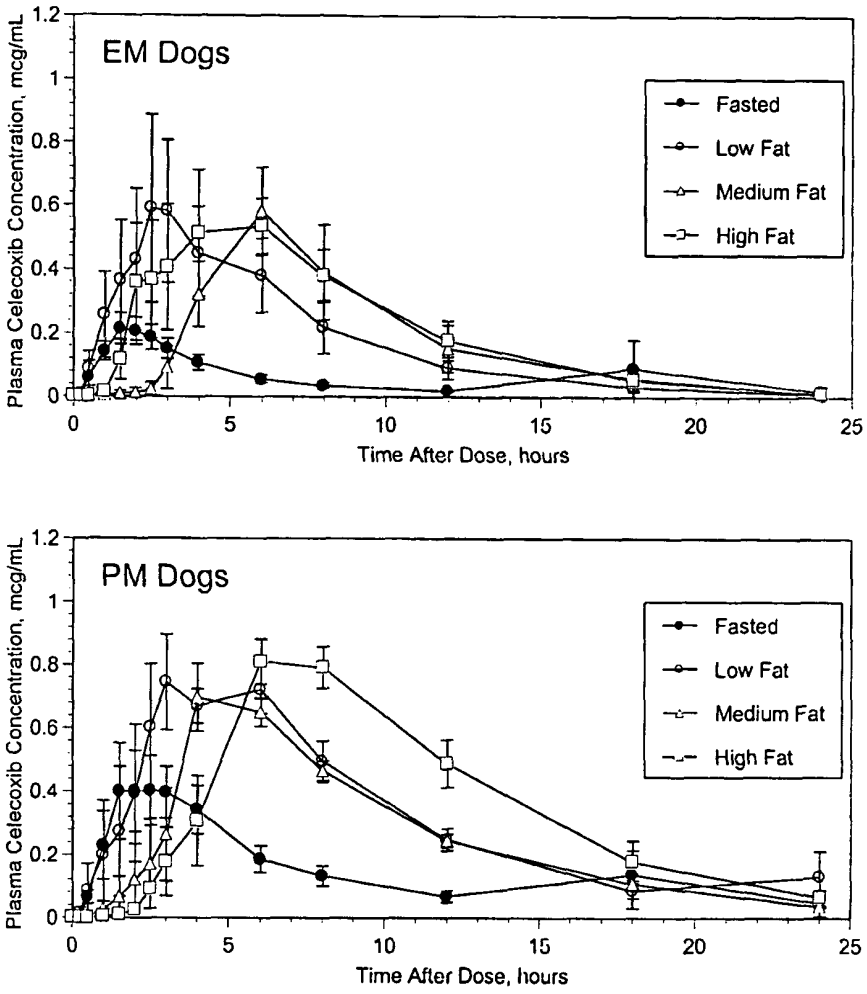

Fig. 4. Mean ± S.E.M. plasma concentrations of celecoxib in EM and PM beagle dogs dosed orally at 5 mg/kg with celecoxib in the fasted state or fed a low-fat, medium-fat, or high-fat diet.

TABLE 3

Mean ± S.E.M. pharmacokinetic parameters for celecoxib following a single oral dose of celecoxib (5 mg/kg as neat chemical in a gelatin capsule) to dogs that were fasted or fed a low-, medium-, or high-fat diet

Diet	No. of Dogs	T_{max}	C_{max}	$AUC_{0-\infty}$	Absolute BA
		h	*μg/ml*	*(μg/ml)h*	*%*
EM dogs					
Fasted	3	1.5 ± 0.3	0.23 ± 0.04	1.7 ± 0.7	27.4 ± 14.6
Low fat	3	3.0 ± 0.5	0.67 ± 0.23	4.1 ± 1.5	59.9 ± 16.1
Medium fat	3	5.3 ± 0.7	0.58 ± 0.14	4.1 ± 1.2	60.4 ± 11.8
High fat	3	4.0 ± 1.2	0.66 ± 0.11	5.0 ± 1.4	74.4 ± 12.1
PM dogs					
Fasted	3	7.5 ± 5.3[a]	0.49 ± 0.10	3.9 ± 0.4	42.2 ± 4.9
Low fat	3	3.8 ± 1.1	0.89 ± 0.05	8.1 ± 0.7	87.5 ± 9.2
Medium fat	3	4.7 ± 0.7	0.76 ± 0.05	6.3 ± 0.3	67.9 ± 2.6
High fat	3	7.3 ± 0.7	0.89 ± 0.03	8.8 ± 0.5	93.7 ± 1.1

[a] Mean T_{max} without the animal that exhibited a "double peak" plasma concentration curve was 2.3 h.

dence intervals, the differences between the mean T_{max}, C_{max}, and $AUC_{0-\infty}$ values obtained under fed or fasting conditions were significant at the 5% level.

Site of Absorption Study in Dogs. Figure 6 shows the plasma concentration-time profiles for celecoxib after oral administration IG or through a CIAP into the duodenum, jejunum, or colon. The pharmacokinetic parameters are in Table 5. The extent of celecoxib absorption was similar following dosing to all four sites (oral, duodenum, jejunum, colon). However, the rate of celecoxib absorption was slower following administration into the colon compared with oral dosing and dosing through CIAP into the duodenum or jejunum.

Discussion

The dog is used extensively to evaluate oral absorption of candidate pharmaceuticals and to facilitate dosage form de-

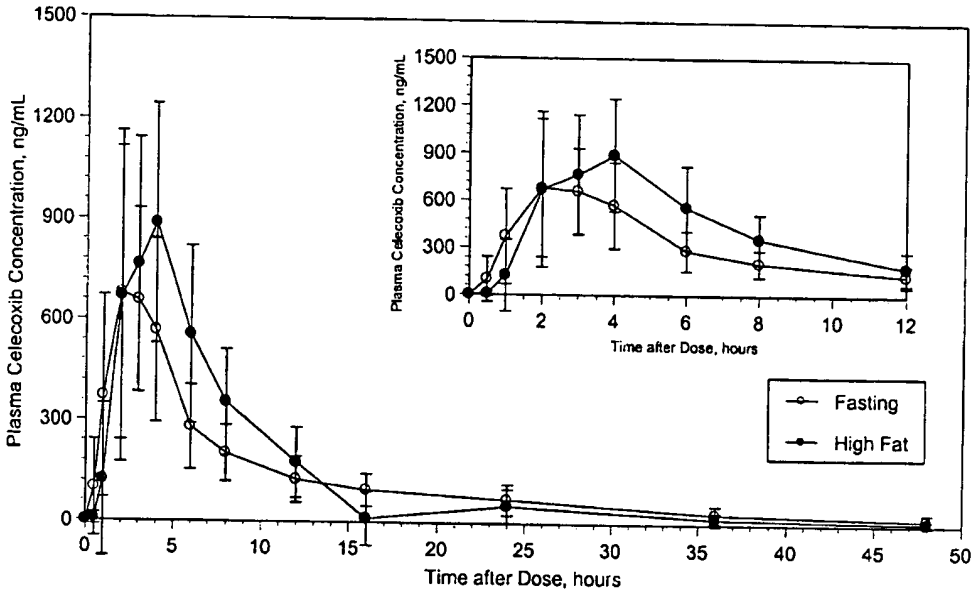

Fig. 5. Mean ± S.D. plasma concentrations of celecoxib in healthy adults administered a single 200-mg celecoxib capsule under fasting conditions or after a high-fat breakfast in a randomized, crossover design study.

TABLE 4

Mean ± S.D. pharmacokinetic parameters for celecoxib following administration of a single oral dose of celecoxib capsule (200 mg) to healthy subjects under fasting conditions or immediately after a high-fat breakfast in a randomized, crossover study

Treatment	No. of Subjects	T_{max}	C_{max}	$AUC_{0-48\ h}$	$AUC_{0-\infty}$	Relative BA
		h	*ng/ml*	*(ng/ml)h*	*(ng/ml)h*	%
Fasted	24	2.44 ± 0.83	806 ± 411	5994 ± 2393	6564 ± 2383	
High-fat breakfast	24	3.42 ± 1.28	1042 ± 355	7141 ± 2887	7318 ± 2818	110.7

velopment. In the present report, the dog was used to study the absorption of celecoxib administered in solution and as a solid, following single and multiple dosing, with and without food, and after administration into different sites of the GI tract.

There is a marked difference in the pharmacokinetic profile for celecoxib when the drug is given orally in solution compared with when it is administered as a solid to dogs. Celecoxib was rapidly absorbed when given orally as a solution with a T_{max} of less than 1 h. The T_{max} for celecoxib was prolonged for another 1 to 2 h when given as a solid. The slower absorption of celecoxib from solid dosage forms was likely due to the time necessary for dispersion and dissolution of celecoxib in the milieu of the GI tract. Celecoxib was well absorbed when given in a solution with an absolute BA of 63.7% for EM dogs and 88.2% for PM dogs. The absolute BA of celecoxib was significantly lower when the drug was given as a solid (21.7% for EM dogs and 39.4% for PM dogs). The near complete absorption of celecoxib from the solution and an octanol/water partition coefficient of greater than 1×10^3 support that celecoxib is a highly permeable drug. The limited absorption of celecoxib as a solid is indicative of a poorly soluble drug with bioavailability that is dissolution rate limited. The aqueous solubility of celecoxib is low at 3 to 7 μg/ml when determined in vitro at pH 7 and 40°C. Since the pK_a of celecoxib is 11.1 the solubility of the drug is likely to also be low at physiological pH. The lower systemic availability in EM dogs is likely a reflection of greater first pass metabolism than in the PM animal.

The regional difference in intestinal absorption of celecoxib was evaluated in conscious dogs using chronic intestinal access ports (Meunier et al., 1993). The properties of the intestine differ throughout its length. The surface area available for absorption is greatest in duodenum with the presence of the microvilli and lowest in the colon. Transit time is 3 to 4 h in the small intestine and can be up to 24 h in the colon (Davies and Morris, 1993). The observations that the systemic exposure to celecoxib given IG was the same following direct administration into the duodenum, jejunum, and colon support that celecoxib is a highly permeable drug that can be absorbed through the GI tract.

Food had a remarkable effect upon the absorption profile of celecoxib in the dog. Although T_{max} was delayed by food, the absolute BA of celecoxib was increased about 3-fold following administration as a solid to the fed compared with fasted animal. In fact, absolute BA of celecoxib when given with food approached the absolute BA of celecoxib when given as a solution. These data suggest that the effect of food is to enhance the dissolution of celecoxib. The consumption of a meal can have many effects upon the GI physiology that influence drug absorption, especially those compounds that are highly lipophilic (Karim, 1996). Food is known to change gastric motility to a postprandial pattern and to delay gastric emptying (Welling, 1996; Fleisher et al., 1999). Although these changes would likely result in delayed drug absorption due to delayed gastric emptying, the longer gastric residence time would allow more time for dispersion and dissolution of a poorly soluble, lipophilic drug such as celecoxib thereby increasing the extent of absorption. The secretion of bile salts and the larger volume of gastric fluid after a meal may also increase the dissolution rate of poorly soluble drugs. Cyclosporin and griseofulvin are lipophilic drugs whose absorption

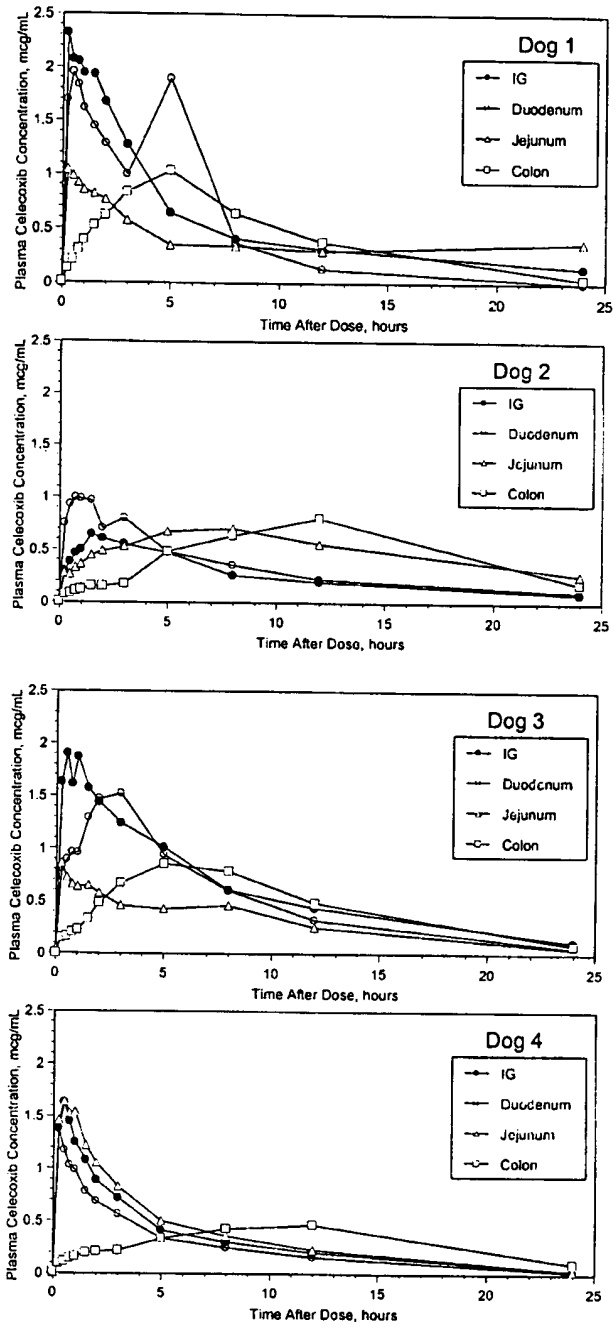

Fig. 6. Individual plasma concentrations of celecoxib in beagle dogs administered 10 mg/kg with celecoxib IG or through a CIAP into the duodenum, jejunum, or colon.

is enhanced by bile salts (Lindholm et al., 1990; Charman et al., 1997).

Unlike dog, a high-fat diet had minimal effect on the extent of celecoxib absorption in humans. The systemic exposure to celecoxib as measured by $AUC_{0-\infty}$ and C_{max} was increased only 10.7 and 25%, respectively, when the drug was given with a high-fat breakfast to healthy subjects. This increase in systemic exposure to celecoxib following administration with food is not clinically relevant. The consumption of a high-fat breakfast also delayed celecoxib absorption in humans resulting in T_{max} values that were 2 to 3 h more prolonged compared with T_{max} values obtained under fasting state; most likely a result of delayed gastric emptying.

The food effects studies in the dogs and humans were conducted under different conditions that could have contributed to the differences in the magnitude of the absorption response to food. The healthy subjects received a 200-mg dose (2.85 mg/kg for a 70-kg body weight) and the dogs received 5 mg/kg (35–70 mg depending on body weight). The dogs were given the celecoxib as neat chemical and the healthy subjects were administered a formulated capsule. However, there was no difference in the bioavailability of celecoxib following administration as neat chemical or in a formulated capsule to EM dogs.

Although the dog is a useful and convenient model for humans there are differences between the two species that may affect an oral pharmacokinetic profile. Under fasting conditions, the gastric emptying time is similar between the two species but the intestinal transit time is twice as long in the human as dog (Dressman, 1986). In humans, the longer intestinal transient time coupled with the ability of celecoxib to be absorbed throughout the GI tract may allow for a complete absorption of the compound under fasting conditions and a minimal change in absorption with food. Whereas, in dogs, a shorter intestinal transient time under fasting conditions would allow less time for dissolution, resulting in incomplete absorption. Consumption of a meal will delay gastric emptying in both species. Compared with humans, the dog has a slower gastric emptying time after feeding (Meyer et al., 1985). The longer gastric residence time, in dogs, after a meal may allow more time for dissolution, resulting in the marked increased in the extent of absorption of celecoxib. Further investigation is needed to fully understand this species difference in food on the absorption of celecoxib.

Celecoxib absorption did not change after multiple dose administration. Systemic exposure to celecoxib in dogs remained constant following daily administration of the drug for up to 1 year.

In conclusion, celecoxib is a poorly soluble, highly permeable drug, i.e., class 2 of the Biopharmaceutical classification

TABLE 5

Mean ± S.E.M. pharmacokinetic parameters for celecoxib after administration of celecoxib (10 mg/kg in a solution) IG or directly through a chronic intestinal access port into the duodenum, jejunum, or colon of beagle dogs

Site	No. of Dogs	T_{max}	C_{max}	$AUC_{0-24\ h}$	$AUC_{0-\infty}$
		h	*μg/ml*	*μg/ml*	*μg/ml*
IG	4	0.69 ± 0.28	1.62 ± 0.36	10.3 ± 2.0	11.3 ± 2.2
Duodenum	4	1.13 ± 0.63	1.46 ± 0.20	9.69 ± 1.57	10.1 ± 1.5
Jejunum	4	2.25 ± 1.92	1.06 ± 0.21	9.37 ± 0.97	12.1 ± 2.2
Colon	4	8.5 ± 2.0	0.79 ± 0.12	10.0 ± 0.9	10.8 ± 1.0

system. The absorption of celecoxib is minimally affected when administered with food in humans. Therefore, for chronic administration patients with arthritis can be given celecoxib with or without food. For acute therapy; however, celecoxib may be preferably given under fasting state to avoid the food-induced lag time in its absorption.

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